IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent No. 6,039,931:

Issued: March 21, 2000

Inventors: Heribert Schmitt-Willich; Johannes Platzek; Heinz Gries; Gabrielle Schumann-Giampieri; Hanns-Joachim Weinmann; Hubert Vogler; Julius Deutsch; and Juergen Conrad

Assignee: Bayer Schering Pharma Aktiengesellschaft

Title: DERIVATIZED DTPA COMPLEXES, PHARMACEUTICAL AGENTS CONTAINING THESE COMPOUNDS, THEIR USE, AND PROCESSES FOR THEIR PRODUCTION

Mail Stop: Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPLICATION FOR EXTENSION OF TERM UNDER 35 U.S.C. §156

SIR:

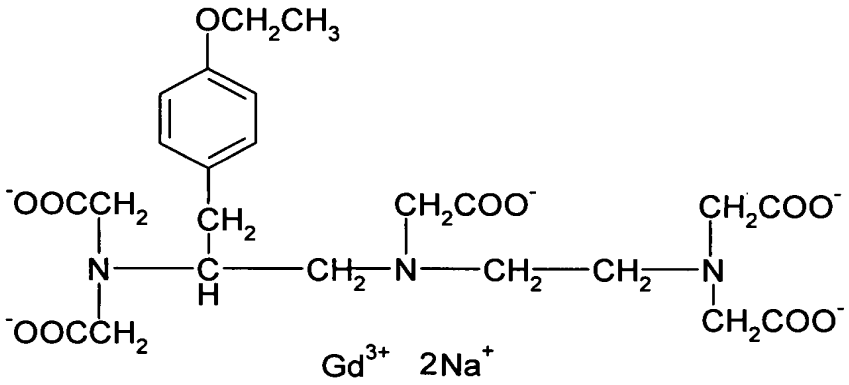
Applicant, Bayer Schering Pharma Aktiengesellschaft, a corporation organized and existing under and by virtue of the laws of Germany, and having a principal place of business at Muellerstrasse 170-178, Berlin 13342, Germany represents that it is the assignee of the entire interest in and to letters patent of the United States No. 6,039,931 granted to Heribert Schmitt-Willich, Johannes Platzek, Heinz Gries, Gabrielle Schumann-Giampieri, Hanns-Joachim Weinmann, Hubert Vogler, Julius Deutsch, and Juergen Conrad on March 21, 2000, for "Derivatized DTPA complexes, pharmaceutical agents containing these compounds, their use, and processes for their production". An assignment of said patent was executed in the name of Schering Aktiengesellschaft and was recorded in the U.S. Patent and Trademark

Office on Reel 6568/ Frame 0496, and a name change from Schering Aktiengesellschaft to Bayer Schering Pharma Aktiengesellschaft was recorded in the U.S. Patent and Trademark Office on Reel 020156, Frame 0001.

EOVIST™ is a gadolinium-based contrast agent, for intravenous use in magnetic resonance imaging (MRI), also known as nuclear magnetic imaging, of the liver. The active ingredient of EOVIST™ is gadoxetate disodium, the use of which in magnetic resonance imaging falls within the ambit of the claims of U.S. Patent 6,039,931. Bayer Schering Pharma Aktiengesellschaft was granted approval by the Food and Drug Administration for commercial marketing or use of EOVIST™ on July 3, 2008.

Applicant, acting through its duly authorized attorney, hereby submits this application for extension of patent term under 35 U.S.C. §156 by providing the following information required by the rules promulgated by the U.S. Patent and Trademark Office (37 C.F.R. §1.710-1.785). For the convenience of the U.S. Patent and Trademark Office, the information presented in this application is in a format which follows the requirements of 37 C.F.R. §1.740(a).

(1) EOVIST™ contains as the active ingredient gadoxetate disodium (aka Gd-EOB-DTPA) ($GdC_{23}H_{28}N_3O_{11}Na_2$), whose chemical name is (4S)-4-(4-Ethoxybenzyl)-3,6,9-tris(carboxylatomethyl)-3,6,9-triazaundecanedioic acid, gadolinium complex, disodium salt. Gadoxetate disodium has the CAS registry number 135326-22-6 and the following structural formula:



(2) The approved product, EOVIST™, was subject to regulatory review under the Federal Food, Drug and Cosmetic Act Section 505 (21 U.S.C. §355).

(3) The approved product, EOVIST™, received permission for commercial marketing or use under Section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. §355) on July 3, 2008 (NDA-22-090).

(4) The only active ingredient in EOVIST™ is gadoxetate disodium which has not been approved for commercial marketing or use under Section 505 or any other section of the Federal Food, Drug and Cosmetic Act prior to the approval of NDA-20-090 by the Food and Drug Administration. It has also not been previously approved for commercial marketing or use under the Public Health Act or the Virus-Serum-Toxin Act.

(5) This application for extension of patent term under 35 U.S.C. 156 is being submitted within the permitted 60 day period pursuant to 37 C.F.R. §1.720(f), which period is believed to expire on August 31, 2008.

(6) The complete identification of the patent for which extension is being sought is as follows:

Inventors:	Heribert Schmitt-Willich, Johannes Platzek, Heinz Gries, Gabrielle Schumann-Giampieri, Hanns-Joachim Weinmann, Hubert Vogler, Julius Deutsch, and Juergen Conrad
Patent Number:	6,039,931
Issue Date:	March 21, 2000
Expiration Date:	March 21, 2017

(7) See "Attachment A" for a complete copy of the patent identified in paragraph (6) hereof.

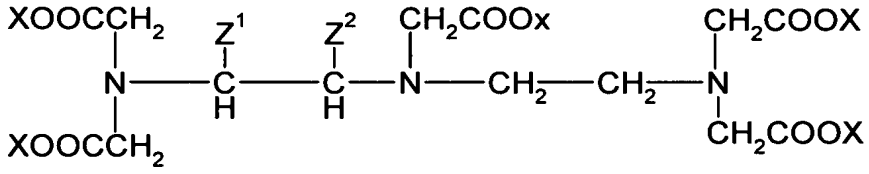
(8) A certificate of correction was issued with regard to U.S. Patent 6,039,931 on April 9, 2002. In addition, the maintenance fees for the 4th and 8th years have been paid for U.S. Patent 6,039,931. No Terminal Disclaimer or re-examination certificate has been issued with regard to U.S. Patent 6,039,931. Attached as "Attachment B" is a copy of the certificate of correction issued April 9, 2002 with regard to U.S. Patent 6,039,931, as well as copies of the Maintenance Fee Statements showing that the 4th and 8th year maintenance fee payments have been made with respect to U.S. Patent 6,039,931.

(9) U.S. Patent 6,039,931 claims the use of the approved product EOVIST™ in methods of nuclear magnetic resonance (NMR) imaging and methods of enhancing NMR

imaging. Specifically, methods of using the approved product EOVIST™ are covered under claims 1, 3-5, 8, 9,11, 13, 14, 18, 19, 21, 24-26, 28-30, and 35 which follow:

Claims:

1. A method of enhancing an NMR image comprising administering to a patient a compound of the formula



wherein

one of Z^1 and Z^2 is H and the other is

$-(CH_2)_m-(C_6H_4)_q-(O)_k-(CH_2)_n-(C_6H_4)_l-(O)_r-R$,

wherein

m and n, independently, are each 0-20,

k, l, q and r are each, independently, 0 or 1,

R is H, C_1-C_6-alkyl, OR^1-substituted C_1-C_6-alkyl or CH_2COOR^1,

R^1 is H, C_1-C_6-alkyl or benzyl; and

X is, in each case, a hydrogen atom or a metal ion equivalent of an element of atomic number 21-29, 42, 44 or 58-70;

with the provisos that:

at least two X groups represent a metal ion equivalent of atomic number 21-29, 42, 44 or 58-70;

when n and l are each 0, then k and r are not each simultaneously 1;

$-(O)_r$ -R is not -OH;

Z^1 and Z^2 are not $-C_6H_5$, $-CH_2-C_6H_5$, $-CH_2-C_6H_4-O-CH_2-COOCH_2C_6H_5$ or $-CH_2-C_6H_4-O-(CH_2)_5-COOCH_2C_6H_5$; and

at least one of q and l is 1; or

a physiologically acceptable salt thereof with an inorganic and/or organic base, an amino acid or an amino acid amide.

3. A method of claim 1, wherein Z^2 is hydrogen and Z^1 is $-(CH_2)_m-(C_6H_4)_q-(O)_k-(CH_2)_n-(C_6H_4)_l-(O)_r-R$, which is not hydrogen.

4. A method of claim 1, wherein Z^1 is $-CH_2-C_6H_4-OCH_3$, $-CH_2-C_6H_4-O-CH_2-C_6H_4-OCH_3$, $-CH_2-O-CH_2-C_6H_5$, $-CH_2-C_6H_4-O-CH_2-COOH$, $-CH_2-C_6H_4-OC_2H_5$, $-CH_2-C_6H_4-OC_4H_9$ or $-CH_2-C_6H_4-O-CH_2-C_6H_5$.

5. A method of claim 4, wherein Z^1 is $-CH_2-C_6H_4-OCH_3$, $-CH_2-C_6H_4-O-CH_2-C_6H_4-OCH_3$, $-CH_2-O-CH_2-C_6H_5$, or $-CH_2-C_6H_4-O-CH_2-COOH$.

8. A method of claim 1, wherein at least three X groups represent a Gd ion.

9. A method of claim 4, wherein at least three X groups represent a Gd ion.

11. A method of claim 1, wherein said compound is:

gadolinium complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-methoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

europium complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-methoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

iron(III) complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-methoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

gadolinium complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-5-(4-methoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

gadolinium complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-[4-(4-methoxybenzyloxy)benzyl]undecanedioic acid or a physiologically acceptable salt thereof;

gadolinium complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-benzyloxymethylundecanedioic acid or a physiologically acceptable salt thereof;

gadolinium complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-carboxymethoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

gadolinium complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-ethoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

europium complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-ethoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof,

iron complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-ethoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

gadolinium complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-butoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

europium complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-butoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

iron complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)4-(4-butoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof,

gadolinium complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-benzyloxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

europium complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-benzyloxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

iron complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-benzyloxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof.

13. A method of claim 1 wherein the hepatobiliary system is imaged.

14. A method according to claim 1, wherein two of the X groups represent manganese(II), iron(II), cobalt(II) or copper(II); or three of the X groups represent chromium(III), praseodymium(III), neodymium(III), samarium(III), ytterbium(III), gadolinium(III), terbium(III), dysprosium(III), holmium(III), erbium(III), or iron(III)

18. A method according to claim 1, wherein R is C_{1-6}-alkyl or C_{1-6}-alkyl substituted by $-OR_1$.

19. A method according to claim 1, wherein one of Z^1 and Z^2 is $-CH_2-C_6H_4-O-(CH_2)_n-(C_6H_4)_l-(O)_r-R$.

21. A method according to claim 1, wherein the X groups which do not represent a metal ion equivalent of atomic number 21-29, 42, 44 or 57-83 are individually lithium, potassium or sodium, or two such X groups are calcium or magnesium.

24. A method according to claim 1, wherein said compound is administered in a dose of 1 μmole/kg-5 mmole/kg.

25. A method according to claim 24, wherein the dose of said compound is 10 μmole/kg-0.5 mmole/kg.

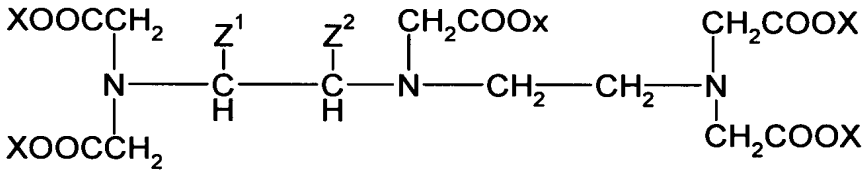
26. A method according to claim 1, wherein said compound is administered by intravenous injection.

28. A method according to claim 1, wherein at least one of k and r is 1.

29. A method according to claim 1, wherein said compound is administered as a pharmaceutical composition comprising said compound and a pharmaceutically acceptable carrier.

30. A method according to claim 1, wherein R^1 is H or C_1-C_6-alkyl.

35. In a method of NMR imaging a patient comprising administering an NMR contrast agent to said patient, the improvement wherein said contrast agent is a compound of the formula



wherein

one of Z^1 and Z^2 is H and the other is

$-(CH_2)_m-(C_6H_4)_q-(O)_k-(CH_2)_n-(C_6H_4)_l-(O)_r-R$,

wherein

m and n, independently, are each 0-20,

k, l, q and r are each, independently, 0 or 1,

R is H, C_1-C_6-alkyl, OR^1-substituted C_1-C_6-alkyl or CH_2COOR^1,

R^1 is H, C_1-C_6-alkyl or benzyl; and

X is, in each case, a hydrogen atom or a metal ion equivalent of an element of atomic number 21-29, 42, 44 or 58-70;

with the provisos that:

at least two X groups represent a metal ion equivalent of atomic number 21-29, 42, 44 or 58-70;

when n and l are each 0, then k and r are not each simultaneously 1;

$-(O)_r$ -R is not -OH;

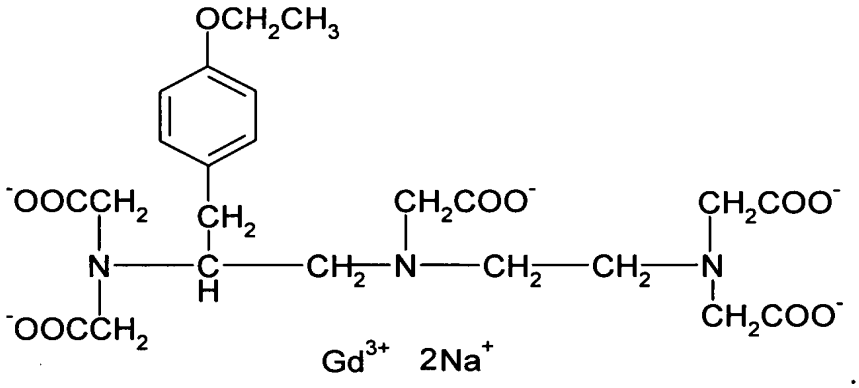
Z^1 and Z^2 are not $-C_6H_5$, $-CH_2-C_6H_5$, $-CH_2-C_6H_4-O-CH_2-COOCH_2C_6H_5$ or $-CH_2-C_6H_4-O-(CH_2)_5-COOCH_2C_6H_5$; and

at least one of q and l is 1;

or a physiologically acceptable salt thereof with an inorganic and/or organic base, an amino acid or an amino acid amide.

Demonstration of the manner in which the claims read on the method of using the approved product:

Gadoxetate disodium has the following structural formula



This structure falls within the scope of method claims 1, 30, and 35, wherein Z^1 is $-CH_2-C_6H_4-OC_2H_5$ (e.g., Z^1 is $-(CH_2)_m-(C_6H_4)_q-(O)_k-(CH_2)_n-(C_6H_4)_l-(O)_r-R$, m is 1, q is 1, one of k and r is 1 and the other is 0, n is 0, l is 0, and R is C_2-alkyl), Z^2 is H, three of the X's are Gd^{+3}, and two of the X's are each Na^+.

Gadoxetate disodium falls within the scope of claims 3-5, and 19 because Z^1 is $-CH_2-C_6H_4-OC_2H_5$ and Z^2 is H.

Gadoxetate disodium falls within the scope of claims 8, 9, and 14 because three of the X's are Gd^{+3}.

Gadoxetate disodium falls within the scope of claim 11 because gadoxetate disodium is a physiologically acctpable salt of the gadolinium complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-ethoxybenzyl)undecanedioic acid.

The use of EOVIST™ in nuclear magnetic imaging of the liver is encompassed by claim 13, since the liver is part of the hepatobiliary system (see, e.g., Dorland's Illustrated Medical Dictionary, 26th Edition, p. 599 (1981)).

Gadoxetate disodium falls within the scope of claim 18 because R is C_2-alkyl.

Gadoxetate disodium falls within the scope of claim 21 because two of the X's are each Na^{+1}.

Claims 24-26, 29, and 32 each encompass use of the product EOVIST™. EOVIST™ is in the form of a solution for intravenous injection and the recommend dosage is 25 μmole/kg. Thus, EOVIST™ can be used to administer gadoxetate disodium intravenously in an amount of 1 μmole/kg-5 mmole/kg, or 10 μmole/kg-0.5 mmole/kg.

(10) The relevant dates and information pursuant to 35 U.S.C. §156(g) to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(A) The Investigational New Drug Application (IND-54,875) for gadoxetate disodium was filed December 19, 1997 and is believed to have become effective on January 19, 1998.

(B) The New Drug Application (NDA-22-090) for EOVIST™ was initially submitted to the FDA on June 29, 2007.

(C) The New Drug Application (NDA-22-090) for EOVIST™ was approved on July 3, 2008.

(11) A brief description of the significant activities undertaken by Applicant during the applicable regulatory review period is attached hereto as "Attachment C" and the dates applicable to such activities.

(12)(A) Applicant is of the opinion that U.S. Patent 6,039,931 is eligible for extension under 35 U.S.C. §156 because it satisfies all of the following requirements for such extension:

(a) 35 U.S.C. §156(a); 37 C.F.R. §1.720(a)

U.S. Patent 6,039,931 claims a method of using a product as defined in 37 C.F.R. §1.710(b)(1);

(b) 35 U.S.C. §156(a)(2); 37 C.F.R. §1.720(b)

The term of U.S. Patent 6,039,931 has never been previously extended;

(c) 35 U.S.C. §156(a)(3); 37 C.F.R. §1.730

This application for extension is submitted by the patent owner of record, in accordance with the requirement of 35 U.S.C. §156(d) and the rules of the U.S. Patent and Trademark Office, and signed by a registered practitioner on behalf of the patent owner ;

(d) 35 U.S.C. §156(a)(4); 37 C.F.R. §1.720(d)

The product EOVIST™ has been subject to a regulatory review period as defined in 35 U.S.C. §156(g) before its commercial marketing or use;

(e) 35 U.S.C. §156(a)(5)(A); 37 C.F.R. §1.720(e)(i)

The commercial marketing or use of the product EOVIST™ after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug and Cosmetics Act (21 U.S.C. 360) under which such regulatory review period occurred;

(f) 35 U.S.C. §156(d)(1); 37 C.F.R. §1.720(f)

The application is submitted within the permitted 60 day period beginning on the date the product first received permission for commercial marketing or use;

(g) 35 U.S.C. §156(a)(1); 37 C.F.R. §1.720(g)

The term of U.S. Patent 6,039,931 has not expired before submission of this application;

(h) 35 U.S.C. §156(c)(4); 37 C.F.R. §1.720(h)

No other patent has been extended for the same regulatory review period for the product EOVIST™.

(12)(B) Applicant is further of the opinion that the patent term U.S. Patent 6,039,931 for EOVIST™ is eligible for an extension under 35 U.S.C. §156 of 1699 days. The length of extension was determined pursuant to 37 C.F.R. §1.775 as follow:

(1) Determination of the length of the Regulatory Review Period

(i) The regulatory review period under 35 U.S.C. §156(g)(1)(B) began December 19, 1997 and ended July 3, 2008, which is a total of 3850 days which is the sum of (ii) and (iii) below;

(ii) The period of review under 35 U.S.C. §156(g)(1)(B)(i), the IND period, began on December 19, 1997 and ended on June 29, 2007, which is 3479 days.

(iii) The period of review under 35 U.S.C. §156(g)(1)(B)(ii), the "Application Period," began on June 29, 2007 and ended July 3, 2008, which is 371 days.

(2) Determination of the length of the Regulatory Review Period upon which the period of extension is calculated is the entire regulatory review period as determined in subparagraph 12(B)(1)(i) (3850 days) less

(i) The number of days in the regulatory review period which were on or before the date on which the patent issued (March 21, 2000), which is 823 days, and

(ii) The number of days during which applicant did not act with due diligence, which is zero (0) days, and

(iii) One-half the number of days determined in subparagraph 12(B)(1)(ii) after subtracting there from the number of days of subparagraphs (12)(B)(2)(i)and (12)(B)(2)(ii) or 1328 days (i.e., ½(3479-823-0),

which totals 1699 days (i.e., 3850-823-½(3479-823+0).

(3) The number of days as determined in subparagraph 12(B)(2) (1699 days) when added to the original term of the patent would result in the date November 14, 2021.

(4) Fourteen (14 years) when added to the date of the NDA approval (July 3, 2008) would result in the date July 3, 2022.

(5) The earliest date as determined in paragraphs 12(B)(3) and 12(B)(4) is November 14, 2021.

(6) The issuance of the original exemption occurred after September 24, 1984. Five (5) years when added to the original expiration date of the patent (March 21, 2017) would result in the date March 21, 2022.

(7) The earlier date as determined in paragraphs 12(B)(5) and 12(B)(6) is November 14, 2021.

Therefore, the length of extension of patent term claimed by applicant is 1699 days or four (4) years and 243 days.

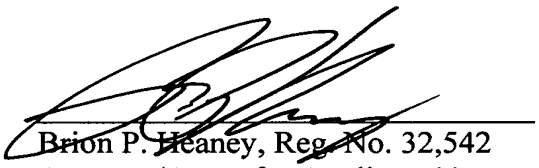
(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any Information which is material to the determination of entitlement to the extension sought.

(14) The prescribed fee of $1,120 pursuant to 37 C.F.R. §1.20(j) for receiving and acting upon this application is to be charged to the counsel's Deposit Account 13-3402.

(15) All inquiries and correspondence relating to this application are to be directed to the undersigned.

Pursuant to 37 C.F.R. §1.740(b), two copies of these application papers, certified as such, are being submitted herewith.

Respectfully submitted,



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Date: August 29, 2008

ATTACHMENT A

1. **Complete copy of US Patent No. 6,039,931**

US006039931A

United States Patent [19]

Schmitt-Willich et al.

[11] Patent Number: 6,039,931

[45] Date of Patent: Mar. 21, 2000

[54] **DERIVATIZED DTPA COMPLEXES, PHARMACEUTICAL AGENTS CONTAINING THESE COMPOUNDS, THEIR USE, AND PROCESSES FOR THEIR PRODUCTION**

[75] Inventors: **Heribert Schmitt-Willich; Johannes Platzek; Heinz Gries; Gabrielle Schumann-Giampieri; Hanns-Joachim Weinmann; Hubert Vogler; Julius Deutsch; Juergen Conrad,** all of Berlin, Germany

[73] Assignee: **Schering Aktiengesellschaft,** Berlin, Germany

[21] Appl. No.: **08/319,357**

[22] Filed: **Oct. 6, 1994**

Related U.S. Application Data

[62] Division of application No. 07/909,379, Jul. 6, 1992, abandoned, which is a continuation of application No. 07/809,830, Dec. 20, 1991, abandoned, which is a continuation of application No. 07/780,840, Oct. 23, 1991, abandoned, which is a continuation-in-part of application No. 07/544,530, Jun. 28, 1990, abandoned.

[30] **Foreign Application Priority Data**

Jun. 30, 1989 [DE] Germany 39 22 005

[51] **Int. Cl.**[7] **A61K 49/00**; C07F 5/00

[52] **U.S. Cl.** **424/9.364**; 534/16

[58] **Field of Search** 534/15, 16; 424/9, 424/9.364

[56] **References Cited**

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0 315 220	5/1989	European Pat. Off. .	
37 10 730	10/1988	Germany .	
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89/05802	6/1989	WIPO .	

Primary Examiner—John Kight
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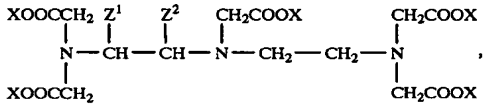
Attorney, Agent, or Firm—Millen, White, Zelano, & Branigan, P.C.

[57] **ABSTRACT**

Compounds of general Formula I

(I)



wherein

Z^1 and Z^2 in each case independently mean the residue

$$—(CH_2)_m—(C_6H_4)_q—(O)_k—(CH_2)_n—(C_6H_4)_r—(O)_l—R,$$

wherein

m and n means the numbers 0–20,

k, l, q and r means the numbers 0 and 1, and

R means a hydrogen atom, an optionally OR^1-substituted C_1–C_6-alkyl residue, or a CH_2COOR^1 group with R^1 meaning it hydrogen atom, a C_1–C_6-alkyl residue, or a benzyl group,

X means a hydrogen atom and/or a metal ion equivalent of an element of atomic number 21–29, 42, 44 or 57–83,

with the provisos that at least two the substituents X stand for a metal ion equivalent; that one of the substituents Z^1 and Z^2 stands for a hydrogen and the other is not H; that—if n and l each mean the number 0—k and r do not simultaneously mean the number 1; that $—(O)_r—R$ is not —OH; and that Z^1 and Z^2 are not $—CH_2—C_6H_4—O—CH_2—COOCH_2C_6H_5$ or $—CH_2—C_6H_4—O—(CH_2)_5—COOCH_2C_6H_5$, as well as their salts with inorganic and/or organic bases, amino acids or amino acid amides, are valuable pharmaceutical agents, e.g., for NMR.

35 Claims, No Drawings

DERIVATIZED DTPA COMPLEXES, PHARMACEUTICAL AGENTS CONTAINING THESE COMPOUNDS, THEIR USE, AND PROCESSES FOR THEIR PRODUCTION

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a division of application Ser. No. 07/909,379, filed Jul. 6, 1992 (now abandoned), which is a continuation of Ser. No. 07/809,830, filed Dec. 20, 1991 (now abandoned), which is a continuation of Ser. No. 07/780,840, filed Oct. 23, 1991 (now abandoned), which is a continuation-in-part of Ser. No. 07/544,530, filed Jun. 28, 1990 (now abandoned).

BACKGROUND OF THE INVENTION

The invention relates to novel complexes and complex salts, agents containing these compounds, their use in diagnostics and therapy, as well as processes for preparing these compounds and agents.

Metallic complexes have been scrutinized as early as at the beginning of the fifties as contrast media for radiology. The compounds then employed were, however, of such toxicity that utilization on human patients could not be considered. It was, therefore, entirely surprising to find that certain complex salts exhibit adequate compatibility for considering routine administration to human patients for diagnostic purposes. The first representative of this class of compounds was the dimeglumine salt of Gd DTPA [gadolinium(III) complex of diethylenetriaminepentaacetic acid] described in the European Patent Application, Publication No. 71564, which proved itself very well in the form of a contrast medium for nuclear spin tomography. This compound has been registered, under the name of "Magnevist", worldwide as the first NMR diagnostic agent.

Contrast media exhibiting an at least partial extrarenal excretion would be desirable, in particular for patients with limited kidney function.

Consequently, there is a need for NMR contrast media exhibiting various pharmacokinetic behaviors.

SUMMARY OF THE INVENTION

The invention makes such compounds and media available, and also provides a process for their production.

The compounds according to this invention display renal elimination as well as excretion with feces.

Surprisingly, elimination via the gallbladder, however, is not the only extrarenal path of elimination: in NMR studies on rats, upon intravenous administration of the compounds of this invention, a contrast enhancement of the gastrointestinal tract has also been unexpectedly observed. The kidneys, as well as implanted tumors, are likewise visualized with improved contrast.

The elimination (secretion) by way of the stomach has the advantage that demarcation of abdominal structures (e.g., the pancreas) from the gastrointestinal tract is made possible, with a simultaneous contrast enhancement of pathological processes (tumors, inflammations). Imaging of the renal system, of the liver and gallbladder, and the bile ducts can moreover likewise be achieved. Besides the improved visualization of ulcers and stomach carcinomas, it is also possible to perform studies regarding gastric acid secretion with the aid of imaging procedures.

Accordingly, by making the compounds of this invention available, help can be extended to patients with renal insufficiency as well as patients suffering from gastrointestinal disorders (at least 10% of the population in the Western industrial countries). Most of these patients, as well as a large number of patients suspected of harboring such disease, must submit to diagnostic tests. At present, two methods suitable for this purpose are utilized above all: Endoscopy and X-ray diagnostics with the aid of barium contrast media.

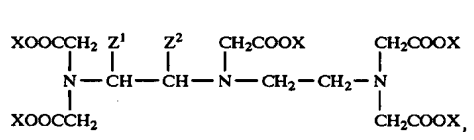
These tests exhibit various drawbacks: they carry the risk of radiation stress, cause trauma, are connected with inconvenience, occasionally even with risk to the patient, and thus can evoke psychological stress. In most instances, these tests must be repeated; their performance is relatively complicated, require the patient's active cooperation (e.g., assumption of a specific bodily attitude) and frequently cannot be employed in case of frail and high-risk patients.

Provision of novel diagnostic methods for the identification and localization of gastrointestinal diseases, which methods do not exhibit these drawbacks, has thus likewise been attained by the complex compounds and agents according to this invention.

Their pharmacokinetics permits, even without specific measures, an improvement in the diagnosis of numerous diseases. The complexes for the most part are excreted again in unchanged form and rapidly so that, especially also in case of using relatively toxic metallic ions, no damaging effects are observed even at high dosage.

The practical use of the novel complexes is also facilitated by their favorable chemical stability.

The compounds of this invention are characterized by general Formula I



(I)

wherein

Z^1 and Z^2 in each case independently mean the residue

$$-(CH_2)_m-(C_6H_4)_q-(O)_k-(CH_2)_n-(C_6H_4)_r-(O)_l-R,$$

wherein

m and n mean the numbers 0–20,

k, l, q and r mean the numbers 0 and 1, and

R means a hydrogen atom, an optionally OR^1-substituted C_1–C_6-alkyl residue, or a CH_2 $COOR^1$ group with R^1 meaning a hydrogen atom, a C_1–C_6-alkyl residue, or a benzyl group,

X means a hydrogen atom and/or a metal on equivalent of an element of atomic numbers 21–29, 42, 44 or 57–83,

with the proviso that at least two of the substituents X stand for a metal ion equivalent; that one of the substituents Z^1 and Z^2 stands for a hydrogen atom and the other is not H; that—if n and l each mean the number 0—k and r do not each simultaneously mean the nurber 1, that $-(O)_r-R$ is not —OH; and that Z^1 and Z^2 are not $-CH_2-C_6H_4-O-CH_2-COOCH_2C_6H_5$ or $-CH_2-C_6H_4-O-(CH_2)_5-COOCH_2C_6H_5$, as well as their salts with inorganic and/or organic bases, amino acids or amino acid amides.

If the agent of this invention is intended for use in NMR diagnostics, then the central ion of the complex salt must be paramagnetic. These are, in particular, the divalent and

trivalent ions of the elements of atomic numbers 21–29, 42, 44 and 58–70. Suitable ions are, for example, the chromium (III), manganese(II), iron(II), cobalt(II), nickel(II), copper (II), praseodymium(III), neodymium(III), samarium(III) and ytterbium(III) ions. On account of their very strong magnetic moment, the gadolinium(III), terbium(III), dysprosium (III), holmium(III), erbium(III) and iron(III)ions are especially preferred.

If the agent of this invention is meant for X-ray diagnostics, then the central ion must be derived from an element of a higher atomic number in order to obtain adequate absorption of the X-rays. It has been found that suitable diagnostic media for this purpose are those containing a physiologically compatible complex salt with central ions of elements of atomic numbers between 21–29, 42, 44, 57–83; these are, for example, the lanthanum(III) ion and the above-cited ions of the lanthanide series.

The numbers standing for m and n are preferably 0 to 5.

Suitable as the alkyl substituents R and R^1 are straight-chain or branched hydrocarbons of up to 6, preferably up to 4 carbon atoms which, in case of R, are optionally substituted by one or several, preferably 1–3, hydroxy or C_1–C_6-, preferably C_1–C_4-alkoxy groups.

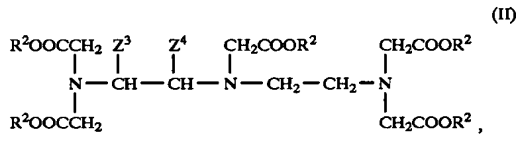
Examples that can be cited for optionally substituted alkyl groups are the methyl, hydroxymethyl, ethyl, 2-hydroxyethyl, 2-hydroxy-1-(hydroxymethyl)ethyl, 1-(hydroxymethyl)ethyl, propyl, isopropyl, 2- and 3-hydroxypropyl, 2,3-dihydroxypropyl, n-, sec- and tert-butyl, 2-, 3- and 4-hydroxybutyl, 2- and 3-hydroxyisobutyl, pentyl, 2-, 3- and 4-hydroxy-2-methylbutyl, 2,3,4-trihydroxybutyl, 1,2,4-trihydroxybutyl, cyclopentyl, cyclohexyl, 2,3,4,5,6-pentahydroxyhexyl groups as well as—in case of the hydroxyalkyl groups—their C_1–C_6-, preferably C_1–C_4-alkyl derivatives, i.e., the corresponding C_{1-6}-alkoxy groups.

Preferred substituents Z^1 and Z^2 are the —CH_2—C_6H_4—OCH_3, —CH_2—C_6H_5, —CH_2—C_6H_4—O—CH_2—C_6H_4—OCH_3, —CH_2—O—CH_2—C_6H_5, —CH_2—C_6H_4—O—CH_2—COOH, —CH_2—C_6H_4—OC_2H_5, —CH_2—C_6H_4—OC_4H_9, —CH_2—C_6H_4—O—CH_2—C_6H_5 residues. Thus, m preferably is 1, and/or q preferably is l, k and/or r preferably is 1, etc., and two phenyl rings are preferably separated by —O—CH_2. etc.

In case not all of the acidic hydrogen atoms are substituted by the central ion, it is possible to replace one, several, or all remaining hydrogen atom(s) by cations of inorganic and/or organic bases or amino acids.

Suitable inorganic cations are, for example, the lithium ion, the potassium ion, the calcium ion, the magnesium ion and, in particular, the sodium ion. Suitable cations of organic bases are, inter alia, those of primary, secondary or tertiary amines, such as, for example, ethanolamine, diethanolamine, morpholine, glucamine, N,N-dimethyglucamine and, in particular, N-methylglucamine. Suitable cations of amino acids are, for example, those of lysine, of arginine, and or ornithine. Suitable cations of amino acid amides are lysine methyl amide, glycine ethyl amide and serine methylamide.

The production of the complex compounds of this invention in accordance with general Formula I takes place by converting, in a manner known per se, compounds of general Formula II



(II)

wherein

R^2 means an acid blocking group,

Z^3 and Z^4 each means a hydrogen atom or the residue —$(CH_2)_m$—$(C_6H_4)_q$—OH, with the proviso that one of the substituents Z^3 and Z^4 is a hydrogen atom and the other is the indicated residue, and m and q are as in Formula I

into a compound with the residue indicated for Z^1 and Z^2, splitting off the acid blocking groups R^2, reacting the thus-obtained complex-forming acids of general Formula I where X is a hydrogen atom (Formula I') with at least one metal oxide or metal salt of an element of atomic numbers 21—29, 42, 44 or 57—83, and subsequently—if desired—substituting any present acidic hydrogen atoms by cations of inorganic and/or organic bases, amino acids or amino acid amides.

Suitable acid blocking groups R^2 are lower alkyl, aryl and aralkyl groups, e.g. the methyl, ethyl, propyl, n-butyl, tert-butyl, phenyl, benzyl, diphenylmethyl, triphenylmethyl, bis (p-nitrophenyl)methyl groups, as well as trialkylsilyl groups.

Splitting off of the blocking groups R^2 takes place according to methods known to one skilled in the art [for example, E. Wünsch, "Methoden der Org. Chemie" [Methods of Organic Chemistry] (Houben-Weyl), vol. XV/1, 4th ed., 1974, pp 315 et seq.], for instance by hydrolysis, hydrogenolysis or alkaline saponification of the esters with an alkali in aqueous-alcoholic solution at temperatures of 0–50° C. Organic or inorganic acids are used for splitting off the tert-butyl esters which are especially advantageous for the present reactions: The ester compound dissolved in a suitable anhydrous organic solvent, but preferably the pulverized dry material, is combined either with a hydrogen halide solution in glacial acetic acid, with trifluoroacetic acid, or also with boron trifluoride diethyl etherate in glacial acetic acid and split off at temperatures of —10° C. to 60° C., preferably at room temperature.

The compounds of general Formula II, serving as educts for the production of the complex compounds of this invention, are known (DOS 3,710,730 and literature cited therein) or can be synthesized analogously to the preparation directions described therein. The entire disclosure of U.S. Ser. No. 07/430,442, now abandoned, (corresponding to the mentioned DOS), of Oct. 2, 1989, is hereby incorporated by reference herein.

A series of literature methods known to a person skilled in the art is available for reacting the known aliphatic or aromatic hydroxy compounds to the corresponding arylalkyl or dialkyl ethers (for example, J. March, Advanced Organic Chemistry, 3rd ed., 1985, pp 342 et seq.).

For this purpose, the compounds of Formula II wherein R^2 stands for an alkali-stable acid blocking group are dissolved in a polar aprotic solvent, such as, for example, tetrahydrofuran, dimethoxyethane or dimethyl sulfoxide, and combined with a base, such as, for example, sodium hydride, sodium hydroxide or alkali or alkaline earth carbonates, at temperatures of between −30° C. and the boiling point of the respective solvent, but preferably between 0° C. and 60° C.

A compound of general Formula III is added to this mixture

$$Y—(CH_2)_n—(C_6H_4)_l—(O)_r—R \quad (III)$$

wherein Y means a nucleofugal entity, such as, for example, Cl, Br, I, $CH_3—C_6H_4SO_3$ or CF_3SO_3, and the remaining indices have the same meanings as in general Formula I.

The reaction periods are 30 minutes to 8 hours, depending on the steric hindrance of the residues participating in the reaction.

As an alternative to the aforedescribed reaction conditions, it is possible to produce arylalkyl as well as dialkyl ethers in a very advantageous way by phase transfer catalysis (Starks and Liotta, Phase Transfer Catalysis, Academic Press, N.Y. 1978, pp. 128—138).

For this purpose, the reaction is performed in a two-phase mixture of an aqueous base, preferably 30% sodium hydroxide solution, and a water-immiscible organic aprotic solvent. Suitable phase transfer catalysts are the compounds known to a person skilled in the art, but preferably tetraalkylammonium or tetraalkylphosphonium salts.

If it is desired to synthesize compounds of general Formula I wherein k, n, l and r=0 and R means a hydrogen atom, then it is possible to conduct the synthesis in analogy to the methods known from the literature, starting with the corresponding unsubstituted amino acid (e.g. phenylalanine).

However, if a series of analogous compounds is to be synthesized, then it is recommended to prepare the phenol derivatives described in DOS 3,710,730 and to reductively remove the phenol function in accordance with literature methods known to those skilled in the art. Above all, the reduction of aryl diethyl phosphates with titanium can be cited which can be performed in a very advantageous way also in the presence of ester groups [S. C. Welch et al., J. Org. Chem. 43: 4797—99 (1978) and literature cited therein]. In this procedure, the corresponding aryl diethyl phosphate is first formed from the phenolic educt by reaction with phosphoric acid diethyl ester chloride in a 70—100% yield, preferably by the use of sodium hydride as the base in a polar aprotic solvent. Subsequently, the reduction is performed with freshly prepared titanium metal. Preferably, anhydrous titanium(III) chloride is reduced by magnesium or potassium in anhydrous tetrahydrofuran under an inert gas for preparing highly active titanium.

The above-described diethyl phosphate is added to such a mixture and heated under reflux for 2–24 hours, preferably 6–16 hours. After the reaction is terminated, the mixture is optionally worked up by chromatography. It is also possible to employ the palladium-catalyzed reduction of the corresponding aryl triflates according to S. Cacchi et al., Tetr. Lett. 27: 5541—44 (1986).

The thus-obtained compounds of general Formula I' wherein X means a hydrogen atom represent complexing agents. They can be isolated and purified or can be converted, without isolation, into metal complexes of general Formula I with at least two of the substituents X meaning a metal ion equivalent.

The metal complexes of this invention can be produced in a way disclosed in Patent DE 3,401,052, by dissolving or suspending the metal oxide or a metal salt (e.g., the nitrate, acetate, carbonate, chloride or sulfate) of the element of atomic numbers 21—29, 42, 44 or 58—70 in water and/or a lower alcohol (such as methanol, ethanol or isopropanol) and reacting with a solution or suspension of the equivalent amount of the complex-forming acid of general Formula I' wherein X means a hydrogen atom, preferably at temperatures of between 40° and 100° C., and subsequently—if desired—substituting any present acidic hydrogen atoms of acid groups by cations of inorganic and/or organic bases, amino acids or amino acid amides.

Neutralization is herein effected with the aid of inorganic bases (for example, hydroxides, carbonates or bicarbonates) of, for example, sodium, potassium, lithium, magnesium or calcium and/or with the aid of organic bases, such as, inter alia, primary, secondary and tertiary amines, e.g., ethanolamine, morpholine, glucamine, N-methyl- and N,N-dimethylglucamine, as well as basic amino acids, such as, for example, lysine, arginine and ornithine.

In order to prepare the neutral complex compounds, it is possible, for example, to add to the acidic complex salts in an aqueous solution or suspension such an amount of the desired bases that the neutral point is reached. The resultant solution can subsequently be evaporated to dryness under vacuum. It is frequently advantageous to precipitate the thus-formed neutral salts by adding water-miscible solvents, such as, for example, lower alcohols (methanol, ethanol, isopropanol, and others), lower ketones (acetone and others), polar ethers (tetrahydrofuran, dioxane, 1,2-dimethoxyethane, and others), and to obtain in this way crystallized products which can be readily isolated and easily purified. It proved to be especially advantageous to add the desired base as early as during the complexing to the reaction mixture, thereby saving a process step.

If the acidic complex compounds contain several free acidic groups, then it is frequently expedient to prepare neutral mixed salts containing inorganic as well as organic cations as the counterions.

This can be done, for example, by reacting the complexing acid in an aqueous suspension or solution with the oxide or salt of the element yielding the central ion and with half the amount of an organic base needed for neutralization, isolating the thus-formed complex salt, purifying same if desired, and then combining same for complete neutralization with the required amount of inorganic base. The sequence or adding the bases can also be reversed.

The pharmaceuticals of this invention can be prepared in a likewise conventional way by suspending or dissolving the complex compounds according to the invention—optionally adding the additives customary in galenic pharmacy—in an aqueous medium and then optionally sterilizing the suspension or solution Suitable additives are, for example, physiologically acceptable buffers (e.g. tromethamine), small additions of complexing agents (such as, for example, diethylenetriaminepentaacetic acid) or, if necessary, electrolytes (such as, for example, sodium chloride) or, if necessary, antioxidants, e.g. ascorbic acid.

If, for enteral administration or other purposes, suspensions or solutions of the agents of this invention in water or a physiological saline solution are desirable, they are mixed with one or several auxiliary agent(s) customary in galenic pharmacy (for example methylcellulose, lactose, mannitol) and/or tenside(s), e.g. lecithins, "Tween", "Myrj" and/or flavoring substance(s) for taste improvement (e.g. ethereal oils).

In principle, it is also possible to prepare the pharmaceuticals of this invention even without isolation of the complex salts. In any event, special care must be directed toward effecting the chelate formation so that the salts and salt solutions according to this invention are practically devoid of toxically active metal ions that are not complexed.

This can be ensured, for example, wits; the aid of color indicators, such as xylenol orange, by control titrations during the manufacturing process. Consequently, the inven-

tion also relates to processes for preparing the complex compounds and their salts. The final safety feature resides in purification of the isolated complex salt.

The pharmaceutical agents of this invention can be administered to mammals, including humans, in a dose or 1 μmol/kg to 5 mmol/kg, preferably 10 μmol to 0.5 mmol/kg of the complex salt according to the invention. For intravenous injection, aqueous formulations are utilized with a concentration of 50 μmol/l to 2 mol/l, preferably 100 mmol/l to 1 mol/l. Rectal as well as oral administration is preferably performed with solutions of a concentration of 0.1 mmol/l to 100 mmol/l. The volumes administered are between 5 ml and 2 l, depending on the diagnostic problem.

The agents according to this invention meet the variegated prerequisites for suitability as contrast media. Thus, they are excellently suited, upon enteral or parenteral administration, to improve the information content of the image obtained with the aid of the NMR tomograph, by increasing the signal intensity. They show furthermore the high efficacy necessary for burdening the body with minimum amounts of foreign substances, and the good compatibility required for maintaining the non-invasive character of the tests.

The high water solubility and low osmolality of the agents according to this invention permits the production of highly concentrated solutions so that the volume load on the circulation is maintained within tolerable limits and dilution by body fluids is compensated. Furthermore, the agents of this invention exhibit not only a high stability in vitro but also a surprisingly high stability in vivo so that release or exchange of the—actually toxic—ions not covalently bound in the complexes takes place only extremely gradually within the time wherein the novel contrast media are again entirely eliminated.

The agents of this invention can also be utilized for radiation therapy. Thus, complexes of gadolinium are excellently suited due to the large capture cross section for neutron capture therapy. If the agent of this invention is intended for use in the version of radiation therapy proposed by R. L. Mills et al. [Nature, 336: 787 (1988)], then the central ion must be derived from a Mössbauer isotope, such as, for example, ^{57}Fe or ^{151}Eu.

When administered, the agents of this invention can also be given together with a suitable carrier, such as, for example, serum or physiological saline solution and/or together with a protein, such as, for example, human serum albumin. The dosage herein is dependent on the type of cellular disorder and on the properties of the metal complex utilized.

In certain aspects, this invention can exclude compounds and compositions wherein Z^1 is phenyl and Z^2 is H and aspects wherein, when —(O)$_r$—R is alkoxy, k, l, and q are simultaneously zero.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight.

The entire disclosures of all applications, patents and publications, if any, cited above and below, and of corresponding application Federal Republic of Germany P 39 22 005.2, filed Jun. 30, 1989, now DE 3922005, are hereby incorporated by reference.

EXAMPLE 1

(a) 3,6,9-Triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-4-(4-methoxybenzyl) undecanedioic Acid Di-tert-butyl Diester

At 0° C., 1.56 g (2 millimoles) of 3,6,9-triaza-3,6,9-tris (tert-butoxycarbonylmethyl)-4-(4-hydroxybenzyl) undecanedioic acid di-tert-butyl diester (Example 9f of DOS 3,710,730) is combined in tetrahydrofuran with 66 mg (2.2 mmol) of 80% strength sodium hydride. This mixtrure is combined with 0.31 g (2.2 mmol) of iodomethane and stirred for 30 minutes. Then the solution is combined with water, tetrahydrofuran is removed by distillation, and the aqueous emulsion is extracted with diethyl ether. The organic phase is washed with water, dried over Na_2SO_4, and concentrated.

Yield: 1.55 g (97.6%)

Calculated: C 63.53 H 9.01 N 5.2 Found: C 63.37 H 8.96 N 5.32

(b) 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-(4-methoxybenzyl)undecanedioic Acid

1.27 g (1.6 mmol) of the tert-butyl ester described in Example 1(a) is dissolved in 25 ml of trifluoroacetic acid and stirred for one hour at room temperature. The solution is then combined with diethyl ether, the precipitate is suctioned off, washed with ether and dried at 40° C. under vacuum over phosphorus pentoxide. The crude product is dissolved in water and combined under agitation with active carbon. The mixture is filtered off from the carbon and lyophilized three times to remove residual trifluoroacetic acid.

Yield: 0.62 g (75.4%)

Calculated: C 51.46 H 6.09 N 8.18 Found: C 51.27 H 6.02 N 8.11

(c) Gadolinium Complex of 3,6,9-Triaza-3,6,9-tris (carboxymethyl)-4-(4-methoxybenzyl)undecanedioic Acid

513 mg (1 mmol) of the complexing acid described in Example l(b) is dissolved in about 30 ml of water and combined at 80° C. with 181 mg (0.5 mmol) of Gd_2O_3. After 30 minutes, the almost clear solution is filtered and the filtrate freeze-dried.

Yield: 649 mg (97.2%) based on the anhydrous material

Calculated: C 39.57 H 4.23 N 6.29 Gd 23.55 Found: C 39.47 H 4.29 N 6.21 Gd 23.19

Disodium Salt of the Gadolinium Complex

The complex (500 mg, 0.75 mmol) obtained as described above is dissolved in 10 times the amount of water and combined by means of a microburette with 1.5 ml of a 1 N sodium hydroxide solution.

After freeze-drying, 533 mg of white crystals is obtained.

T_1 relaxation (1/mmol.sec) is

in water 4.54±0.13

in plasma 6.89±0.17

Di-N-methyl-D-glucamine Salt of the Gadolinium Complex

3.34 g (5 mmol) of the gadolinium complex is combined in 40 ml of water in portions with 1.96 g (10 mmol) of N-methyl-D-glucamine under agitation. After the base has been completely dissolved, the product is freeze-dried There remains 5.55 g of a colorless crystalline compound.

H_2O content (Karl Fischer determination): 4.73%

(d) Europium Complex of 3,6,9-Triaza-3,6,9-tris (carboxymethyl)-4-(4-methoxybenzyl)undecanedioic Acid

5.13 g (10 mmol) of the complexing acid described in Example 1(b) is dissolved in about 30 ml of water and combined at 80° C. with 1.76 g (5 mmol) of Eu_2O_3. After 30 minutes, the almost clear solution is filtered and the filtrate freeze-dried.

Yield: 6.62 g

Analysis (based on anhydrous substance) Calculated: C 39.89 H 4.26 N 6.34 Eu 22.94 Found: C 39.71 H 4.38 N 6.17 Eu 22.58

Disodium Salt of the Europium Complex

The complex described above (497 mg, 0.75 mmol) is dissolved in 10 times the quantity of water and combined by means of a microburette with 1.5 ml of a 1 N sodium hydroxide solution. After freeze-drying, 540 mg of white crystals is obtained.

Di-N-methyl-D-glucamine Salt of the Europium Complex

3.31 g (5 mmol) of the europium complex is mixed in 40 ml of water in portions with 1.96 g (10 mmol) of N-methyl-D-glucamine under agitation. After the base has been completely dissolved, the mixture is freeze-dried. There remains 5.63 g of a colorless, crystalline compound.

(e) Iron(III) Complex of 3,6,9-Triaza-3,6,9-tris (carboxymethyl)-4-(4-methoxybenzyl)undecanedioic Acid

5.13 g (10 mmol) of the complexing acid disclosed in Example 1(b) is dissolved in about 30 ml of water and combined at 80° C. with 798 mg (5 mmol) of Fe_2O_3. After 30 minutes, the almost clear solution is filtered and the filtrate freeze-dried.

Yield: 5.66 g

Analysis (based on anhydrous substance): Calculated: C 46.66 H 4.98 N 7.42 Fe 9.86 Found: C 46.71 H 5.03 N 7.38 Fe 9.81

Disodium Salt of the Iron(III) Complex

The complex obtained as described above (425 mg, 0.75 mmol) is dissolved in 10 times the amount of water and combined by means of a microburette with 1.5 ml of a 1 N sodium hydroxide solution. After freeze-drying, 460 mg of white crystals is obtained.

Di-N-methyl-D-glucamine Salt of the Iron(III) Complex

2.83 g (5 mmol) of the iron(III) complex is combined in 40 ml of water in portions with 1.96 g (10 mmol) of N-methyl-D-glucamine under agitation. After the base has been completely dissolved, the solution is freeze-dried. There remains 4.83 g of a colorless, crystalline compound.

Analogously, with bismuth oxide, Bi_2O_3, the bismuth complex is obtained as the disodium salt and, respectively, as the di-N-methyl-D-glucamine salt.

EXAMPLE 2

(a) 3,6,9-Triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-5-(4-methoxybenzyl) undecanedioic Acid Di-tert-butyl Ester

In accordance with the directions given in Example 1(a), 3.9 g (5 mmol) of 3,6,9-triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-5-(4-hydroxybenzyl)undecanedioic acid di-tert-butyl ester (Example 17d in DOS 3,710,730) is reacted to 3.61 g (91% of theory) of the title compound.

Calculated: C 63.53 H 9.01 N 5.29 Found: C 63.59 H 9.07 N 5.27

(b) 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-5-(4-methoxybenzyl)undecanedioic Acid

3.18 g (4 mmol) of the tert-butyl ester described in Example 2(a) is treated in accordance with the directions set forth in Example 1(b) with trifluoroacetic acid and worked up, thus obtaining 1.62 g (79% of theory) of a colorless lyophilized product.

Calculated: C 51.46 H 6.09 N 8.18 Found: C 51.34 H 6.14 N 8.11

(c) Gadolinium Complex of 3,6,9-Triaza-3,6,9-tris (carboxymethyl)-5-(4-methoxybenzyl)undecanedioic Acid

According to the directions in Example 1(c), 1.03 g (2 mmol) of the complex-forming acid described in Example 2(b) is complexed with Gd_2O_3, yielding 1.32 g (99% of theory) of a colorless lyophilized product.

Calculated: C 39.57 H 4.23 N 6.29 Gd 23.55 Found: C 39.51 H 4.19 N 6.25 Gd 23.61

The T_1 relaxation (1/mmol.sec) is

in water 4.17±0.14

in plasma 6.61±0.18

EXAMPLE 3

(a) 3,6,9-Triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-4-[4-(4-methoxybenzyloxy) benzyl]undecanedioic Acid Di-tert-butyl Ester

At 0° C., 1.56 g (2 mmol) of 3,6,9-triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-4-(4-hydroxybenzyl)undecanedioic acid di-tert-butyl ester (Example 9f of DOS 3,710,730) is combined in tetrahydrofuran with 66 mg (2.2 mmol) of 80% strength sodium hydride. To this mixture is added 0.3 ml (2.2 mmol) of 4-methoxybenzyl chloride and the mixture is stirred overnight. The solution is then combined with water, tetrahydrofuran is removed by distillation, and the aqueous emulsion is extracted with diethyl ether. The organic phase is washed with water, dried over Na_2SO_4, and concentrated. The resultant colorless oil is chromatographed on silica gel (ether/hexane 1:1).

Yield: 1.17 g (65% of theory) of a colorless oil.

Calculated: C 65.38 H 8.62 N 4.67 Found: C 65.29 H 8.65 N 4.59

(b) 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-[4-(4-methoxybenzyloxy)benzyl]undecanedioic Acid

1.80 g (2 mmol) of the tert-butyl ester set forth in Example 3(a) is treated analogously to the directions given in Example 1(b) with trifluoroacetic acid and reacted to 905 mg (73% of theory) of colorless, flaky lyophilized product.

Calculated: C 56.21 H 6.02 N 6.78 Found: C 56.10 H 5.98 N 6.82

(c) Gadolinium Complex of 3,6,9-Triaza-3,6,9-tris (carboxymethyl)-4-[4-(4-methoxybenzyloxy) benzyl]-undecanedioic Acid

Analogously to the directions given for Example 1(c), 620 mg (1 mmol) of the complexing acid described in Example 3(b) is complexed and worked up, yielding 758 mg (98% of theory).

Calculated: C 45.01 H 4.43 N 5.43 Gd 20.32 Found: C 44.93 H 4.49 N 5.37 Gd 20.18

The T_1 relaxation (1/mmol.sec) amounts to

in water 4.23±0.16

in plasma 6.99±0.13

EXAMPLE 4

(a) Diethyl Phosphate of 3,6,9-Triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-4-(4-hydroxybenzyl)-undecanedioic Acid Di-tert-butyl Ester

11.2 g (14.36 mmol) of the phenol disclosed in DOS 3,710,730 (Example 9f) is dissolved in 100 ml of absolute tetrahydrofuran (THF). To this mixture is adder 380 mg (15.8 mmol) of sodium hydride (prepared from 50% NaH in paraffin oil by washing three times with 10 ml of THF). After 30 minutes at room temperature, 2.60 g (15.0 mmol) of phosphoric acid diethyl ester chloride is added and the mixture stirred for 24 hours at room temperature.

The solution is diluted with 500 ml of ether and washed three times with 300 ml of 10% sodium hydroxide solution. After drying the organic phase over magnesium sulfate, the product is concentrated under vacuum and the residue purified by flash chromatography (eluent: ether/hexane= 1:1).

Yield: 11.97 g (91% of theory) of a pale-yellow oil.

Calculated: C 59.00 H 8.58 N 4.59 P 3.38 Found: C 58.88 H 8.63 N 4.63 P 3.30

(b) 3,6,9-Triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-4-benzylundecanedioic Acid Di-tert-butyl Ester

A mixture of 1.33 g (8.62 mmol) of anhydrous titanium (III) chloride and 1.02 g (26.09 mmol) of finely chopped potassium in 20 ml of tetrahydrofuran is heated under reflux in an argon atmosphere for one hour.

Within 15 minutes, a solution of 11.5 g (12.55 mmol) of the compound described in Example 4(a) in 50 ml of tetrahydrofuran is added dropwise to this mixture. Then the mixture is heated under reflux for 8 hours, cooled in an ice bath, 20 ml of methanol is gently added, then 100 ml of water is added, and the mixture is extracted three times with 200 ml of ether. The organic phases are dried over magnesium sulfate and concentrated under vacuum. The residue is chromatographed on silica gel (eluent: hexane/ether=2:1), thus obtaining 8.9 g (93% of theory) of the title compound as a colorless oil which crystallizes upon standing.

Calculated: C 64.46 H 9.10 N 5.50 Found: C 64.54 H 9.15 N 5.41

(c) 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-benzylundecanedioic Acid

Analogously to the directions set forth in Example 1(b), 7.64 g (10 mmol) of the tert-butyl ester described in Example 4(b) is reacted to 4.01 g (83% of theory) of the title compound.

Calculated: C 52.17 H 6.05 N 8.69 Found: C 52.23 H 5.99 N 8.73

(d) Gadolinium Complex of 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-benzylundecanedioic Acid

2.42 g (5 mmol) of the complex-forming acid described in Example 4(c) is reacted analogously to the directions given in Example 1(c) to 3.14 g (98.5% of theory) of the title compound, obtaining the gadolinium complex as a colorless, flaky lyophilized product.

Calculated: C 39.55 H 4.11 N 6.59 Gd 24.66 Found: C 39.47 H 4.19 N 6.52 Gd 24.88

The T_1 relaxation (1/mmol.sec) is

in water 4.54±0.13

in plasma 6.89±0.17

Ytterbium Complex of 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-benzylundecanedioic Acid

Analogously to the directions for preparing the gadolinium complex, the corresponding ytterbium complex is obtained by using Yb_2O_3 in place of Gd_2O_3.

EXAMPLE 5

(a) 3,6,9-Triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-4-benzyloxymethylundecanedioic Acid Di-tert-butyl Ester

Within 30 minutes, 7.2 ml (60 mmol) of benzyl bromide is added dropwise at room temperature to a thoroughly stirred suspension of 14.1 g (20 mmol) of 4-hydroxymethyl-3,6,9-triaza-3,6,9-tris(tert-butoxycarbonylmethyl) undecanedioic di-tert-butyl diester described in DOS 3,710,730 (Example 37d) and 0.3 g of tetrabutylammonium hydrogen sulfate in 200 ml of dichloromethane/200 ml of 30% strength sodium hydroxide solution, and the mixture is then agitated for 8 hours.

400 ml of water is added to this suspension; the organic phase is separated and the aqueous phase extracted twice with respectively 150 ml of dichloromethane. After drying the combined organic phases over magnesium sulfate, the product is chromatographed on silica gel (ether/hexane= 1:1), thus obtaining 13.0 g (82% of theory) of the title compound as a colorless oil.

Calculated: C 63.53 H 9.01 N 5.29 Found: C 63.42 H 9.07 N 5.21

(b) 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-benzyloxymethylundecanedioic Acid

Analogously to the directions given for Example 1(b), 7.94 g (10 mmol) of the tert-butyl ester set forth in Example 5(a) is reacted with trifluoroacetic acid to 4.06 g (79% of theory) of the title compound.

Calculated: C 51.46 H 6.09 N 8.18 Found: C 51.51 H 6.06 N 8.12

(c) Gadolinium Complex of 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-benzyloxymethylundecanedioic Acid

In analogy to the directions in Example 1(c), 2.57 g (5 mmol) of the complexing acid described in Example 5(b) is reacted to 3.30 g (98.9% of theory) of the title compound, yielding a colorless, flaky solid.

Calculated: C 39.57 H 4.23 N 6.29 Gd 23.55 Found: C 39.51 H 4.26 N 6.35 Gd 23.27

The T_1 relaxation (1/mmol.sec) is

in water 4.39±0.12

in plasma 6.31±0.15

EXAMPLE 6

(a) 3,6,9-Triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-4-(4-carboxymethoxybenzyl)undecanedioic Acid Bis (tert-butyl) Ester

At 0° C., 23.40 g (30 mmol) of 3,6,9-triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-4-(4-hydroxybenzyl)undecanedioic

acid di-tert-butyl ester (Example 9f of DOS 3,710,730) is combined in tetrahydrofuran with 2.7 g (90 mmol) of 80% strength sodium hydride. To this mixture is dropped 6.25 g (45 mmol) of bromoacetic acid in tetrahydrofuran, and the mixture is stirred for one hour at 0° C. and overnight at room temperature.

The solution is then combined with water, tetrahydrofuran is removed by distillation, and the aqueous phase is extracted with ethyl acetate. The organic phase is dried over sodium sulfate and concentrated.

The residue is chromatographed on silica gel in an eluent mixture of dioxane/methanol/triethylamine (15:4:1); the combined fractions are concentrated and divided between ethyl acetate and 1 N citric acid. The organic phase is then dried over sodium sulfate and concentrated, thus obtaining 21.8 g (87% of theory) as a colorless oil.

Calculated: C 61.63 H 8.54 N 5.01 Found: C 61.62 H 8.62 N 4.95

(b) 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-(4-carboxymethoxybenzyl)undecanedioic Acid

Analogously to the directions given for Example 1(b), 21.0 g (25 mmol) of the tert-butyl ester described in Example 6(a) is reacted to 11.0 g (78.9% of theory) of the title compound.

Calculated: C 49.55 H 5.60 N 7.54 Found: C 49.31 H 5.51 N 7.47

(c) Gadolinium Complex of 3,6,9-Triaza-3,6,9-tris (carboxymethyl)-4-(4-carboxymethoxybenzyl) undecanedioic Acid

5.57 g (10 mmol) of the complex-forming acid described in Example 6(b) is reacted analogously to the directions set forth in Example 1(c) to yield 7.01 g (98.5% of theory) of the title compound.

Calculated: C 38.81 H 3.96 N 5.90 Gd 22.09 Found: C 38.75 H 3.89 N 5.97 Gd 21.93

The T_1 relaxation (1/mmol.sec) is

in water 5.00±0.01

in plasma 7.10±0.08

EXAMPLE 7

Preparation of a Solution of the Sodium Salt of the Gadolinium(III) Complex of 3,6,9-Triaza-3,6,9-tris (carboxymethyl)-4-benzyloxymethylundecanedioic Acid

6.68 g (10 mmol) of the gadolinium complex obtained according to Example 5(c) is dissolved in 70 ml of water pro injectione (p.i.) and combined dropwise with 1 N sodium hydroxide solution until a pH of 7.2 has been reached. After adding 0.02 g of tromethamine, the mixture is filled up to 100 ml with water p.i.; the solution is dispensed into bottles and heat-sterilized.

EXAMPLE 8

(a) 3,6,9-Triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-4-(4-ethoxybenzyl) undecanedioic Acid Di-tert-butyl Diester

At 0° C., 5.85 g (7.5 mmol) of 3,6,9-triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-4-(4-hydroxybenzyl)undecanedioic acid di-tert-butyl diester (Example 9f of DOS 3,710,730) is combined in 100 ml of tetrahydrofuran with 0.30 g (10 mmol) of 80% strength sodium hydride. To this mixture is added 1.56 g (10 mmol) of iodoethane and the mixture is stirred for 3 hours. Then the solution is combined with water, tetrahydrofuran is distilled off, and the aqueous emulsion is extracted with diethyl ether. The crude product obtained after drying over sodium sulfate and concentration of the solvent is chromatographed on silica gel (system: hexane/ether/triethylamine 70:30:5).

Yield: 4.0 g (66%)

Analysis (based on anhydrous material): Calculated: C 63.91 H 9.11 N 5.20 Found: C 63.67 H 9.05 N 5.28

(b) 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-(4-ethoxybenzyl)undecanedioic Acid

3.64 g (4.5 mmol) of the tert-butyl ester disclosed in Example 8(a) is dissolved in 25 ml of trifluoroacetic acid, stirred for one hour at room temperature, and worked up analogously to Example 1(b).

Yield: 1.2 g (50.6%)

Analysis (based on anhydrous substance): Calculated: C 52.36 H 6.13 N 7.97 Found: C 52.21 H 6.39 N 7.84

(c) Disodium Salt of the Gadolinium Complex of 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-(4-ethoxybenzyl)undecanedioic Acid

528 mg (1 mmol) of the complex-forming acid described in the preceding example is dissolved in 40 ml of water and complexed at 80° C. with 181 mg (0.5 mmol) of Gd_2O_3. Then the mixture is neutralized with 2 ml of 1 N NaOH, stirred with activated carbon, filtered, and the filtrate is freeze-dried.

Yield: 700 mg (96.5%)

Analysis (based on anhydrous material): Calculated: C 38.06 H 3.89 Gd 21.67 N 5.79 Na 6.34 Found: C 37.91 H 3.99 Gd 21.30 N 5.69 Na 6.57

The T_1 relaxation (1/mmol.sec) is

in water 5.33±0.13

in plasma 8.69±0.53

Analogously, the corresponding europium complex is obtained with europium oxide, Eu_2O_3.

Calculated: C 38.34 H 3.92 Eu 21.09 N 5.83 Na 6.38 Found: C 38.20 H 4.01 Eu 20.87 N 5.79 Na 6.49

With iron oxide, Fe_2O_3, the corresponding iron complex is obtained analogously:

Calculated: C 44.25 H 4.52 Fe 8.95 N 6.73 Na 7.37 Found: C 44.17 H 4.59 Fe 8.52 N 6.81 Na 7.49

EXAMPLE 9

(a) 3,6,9-Triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-4-(4-butoxybenzyl) undecanedioic Acid Di-tert-butyl Diester

Analogously to Example 8(a), 5.85 g (7.5 mmol) of 3,6,9-triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-4-(4-hydroxybenzyl)undecanedioic acid di-tert-butyl diester (Example 9f of DOS 3,710,730) is reacted with 1.84 g (10 mmol) of 1-iodobutane and worked up as described therein.

Yield: 4.1 g (65.4%)

Analysis (based on anhydrous compound): Calculated: C 64.64 H 9.28 N 5.03 Found: C 64.82 H 9.37 N 4.96.

(b) 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-(4-butoxybenzyl)undecanedioic Acid

3.34 g (4 mmol) of the tert-butyl ester described in Example 9(a) is dissolved in 20 ml of trifluoroacetic acid,

stirred for one hour at room temperature, and worked up analogously to Example 1(b).

Yield: 1.36 g (61.0%)

Analysis (based on anhydrous material): Calculated: C 54.04 H 6.71 N 7.57 Found: C 53.88 H 6.63 N 7.41

(c) Disodium Salt of the Gadolinium Complex of 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-(4-butoxybenzyl)undecanedioic Acid

556 mg (1 mmol) of the complexing acid described in the preceding example is combined with 40 ml of water and complexed at 80° C. with 181 g (0.5 mmol) of Gd_2O_3. The mixture is then neutralized with 2 ml of 1 N NaOH, stirred with activated carbon, filtered, and the filtrate freeze-dried.

Yield: 711 mg (94.3%)

Analysis (based on anhydrous material): Calculated: C 39.83 H 4.28 Gd 20.86 N 5.58 Na 6.10 Found: C 39.61 H 4.35 Gd 20.51 N 5.49 Na 6.17

The T_1 relaxation (1/mmol.sec) is

in water 5.80±0.26

in plasma 14.20±0.98

Analogously, with the use of europium oxide, Eu_2O_3, the corresponding europium complex is obtained:

Calculated: C 40.11 H 4.31 Eu 20.30 N 5.61 Na 6.14 Found: C 39.97 H 4.39 Eu 20.02 N 5.72 Na 6.25

With iron oxide, Fe_2O_3 the corresponding iron complex is analogously obtained:

Calculated: C 46.03 H 4.94 Fe 8.56 N 6.44 Na 7.05 Found: C 45.88 H 5.03 Fe 8.30 N 6.50 Na 7.11

EXAMPLE 10

(a) 3,6,9-Triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-4-(4-benzyloxybenzyl) undecanedioic Acid Di-tert-butyl Diester

Analogously to Example 8(a), 5.85 g (7.5 mmol) of 3,6,9-triaza-3,6,9-tris(tert-butoxycarbonylmethyl)-4-(4-hydroxybenzyl)undecanedioic acid di-tert-butyl diester (Example 9f of DOS 3,710,730) is reacted with 1.71 g (10 mmol) of benzyl bromide and worked up as described therein.

Yield: 4.9 g (75.1%)

Analysis (based on anhydrous substance): Calculated: C 66.25 H 8.69 N 4.83 Found: C 66.14 H 8.77 N 4.83

(b) 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-(4-benzyloxybenzyl)undecanedioic Acid

3.48 g (4 mmol) of the tert-butyl ester disclosed in Example 10(a) is dissolved in 20 ml of trifluoroacetic acid, stirred for one hour at room temperature, and worked up analogously to Example 1(b).

Yield: 1.33 g (56.5%)

Analysis (based on anhydrous material): Calculated: C 57.04 H 5.98 N 7.13 Found: C 56.89 H 6.03 N 7.21

(c) Disodium Salt of the Gadolinium Complex of 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-(4-benzyloxybenzyl)undecanedioic Acid

590 mg (1 mmol) of the complexing acid described in the preceding example is combined with 40 ml of water and 1 ml of 1 N NaOH and complexed at 80° C. with 181 mg (0.5 mmol) of Gd_2O_3. Then the mixture is neutralized furthermore with 1 ml of 1 N NaOH, stirred with active carbon, filtered, and the filtrate freeze-dried.

Yield: 703 mg (89.2%)

Analysis (based on anhydrous material): Calculated: C 42.69 H 3.84 Gd 19.96 N 5.33 Na 5.84 Found: C 42.63 H 3.91 Gd 19.57 N 5.26 Na 5.99

The T_1 relaxation (1/mmol.sec) is

in water 5.81±0.11

in plasma 16.35±1.01

The corresponding europium complex is obtained analogously with europium oxide, Eu_2O_3:

Calculated: C 42.98 H 3.86 Eu 19.42 N 5.37 Na 5.88 Found: C 43.10 H 3.91 Eu 19.13 N 5.27 Na 5.99

With iron oxide, Fe_2O_3, the corresponding iron complex is obtained analogously:

Calculated: C 48.99 H 4.41 Fe 8.14 N 6.12 Na 6.70 Found: C 48.73 H 4.57 Fe 8.29 N 6.03 Na 6.85

EXAMPLE 11

a) 4-Nitro-N-benzyloxycarbonyl-DL-phenylglycine-(2-aminoethyl)-amide-hydrochloride

588.5 g (3 mol) of 4-nitro-DL-phenylglycine, produced according to J. Biochem. (Tokyo) 88(6), 1773, is suspended in 2.5 liters of ethanol. 713.8 g (6 mol) of thionyl chloride is instilled under ice cooling within 90 minutes, refluxed for two hours, and the resulting solution is evaporated to dryness in a vacuum. The residue is dissolved in 5 liters of water, mixed with 5 liters of diethyl ether and brought to pH 8.5 with 1.5 liters of a 1.5 m-sodium carbonate solution. Then, 511.8 g (3 mol) of chloroformic acid benzyl ester and 1.8 liters of 1.5 m-sodium carbonate solution are instilled simultaneously with intensive stirring, so that the pH of the mixture is between 8.2 and 8.6. It is allowed to stir for two hours at room temperature, the organic phase is separated, it is washed neutral with water, dried on sodium sulfate and the filtered solution is evaporated to dryness. The residue is dissolved in 2 liters of methanol, and the solution is instilled slowly in 3.5 liters of ethylenediamine with intensive stirring. It is allowed to stir for 24 hours, evaporates to dryness in a vacuum, the residue is dissolved in 2 liters of hot methanol and the solution is mixed by instillation under cooling with conc. hydrochloric acid until permanent turbidity. It is allowed to crystallize in the ice bath for 24 hours, the precipitate is suctioned off, it is washed with a little ice-cold methanol and it is dried in a vacuum at 40° C.

1022.3 g (90% of theory) of the title compound is obtained as a yellow powder with an uncharacteristic decomposition point.

Analysis: C 52.88 H 5.18 N 13.70 (calculated) 52.61 5.24 13.77 (found)

b) 1,5-Diamino-3-aza-1-(4-nitrophenyl)-pentane

255.5 g (0.625 mol) of the compound obtained under a) is suspended in 650 ml of a solution of hydrobromic acid in glacial acetic acid. It is allowed to stir for 30 minutes at room temperature and the solution is mixed with diethyl ether until permanent turbidity. After stirring overnight, the precipitated hydrobromide is suctioned off, dried and dissolved in 2 liters of water. After treatment with 1.25 liters of AMBERLITE IRA 410 ion exchange material, the filtered solution is evaporated to dryness and dehydrated by codistillation with toluene. The residue is dissolved in 500 ml of tetrahydrofuran and again concentrated by evaporation. Then, 4.5 liters of a one-molar diborane-tetrahydrofuran complex solution in tetrahydrofuran (ALDRICH) is added and refluxed for 72 hours. After cooling off the solution, 500

ml of methanol is carefully instilled and saturated under ice cooling with hydrochloric acid. It is allowed to stir for four more hours, the precipitate is suctioned off and dried in a vacuum after washing with tetrahydrofuran at room temperature. 170.9 g of the title compound is obtained as trihydrochloride of equivalent weight 113.4 (calculated: 111.2).

c) 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-(4-nitrophenyl)-undecanedioic Acid

58.4 g (175 mmol) of the compound obtained under b) is dissolved in 630 ml of water and 420 ml of a 10 molar potassium hydroxide solution, mixed with 1.1 liters of tetrahydrofuran and, after the addition of 165.4 g (1.75 mol) of chloroacetic acid, stirred for 72 hours at 50° C. It is cooled off to room temperature, the aqueous phase is separated, neutralized with conc. hydrochloric acid, and the solution is evaporated to dryness in a vacuum. The residue is dehydrated by codistillation with toluene, 2 liters of ethanol is added and 312.3 g of thionyl chloride is instilled under ice cooling. It is refluxed for five hours, evaporated to dryness in a vacuum and the residue is mixed with 2 liters of ethyl acetate and 4 liters of a one-molar sodium bicarbonate solution. It is allowed to stir for two hours, the organic phase is separated, it is washed with water, dried on sodium sulfate, filtered and evaporated to dryness in a vacuum. The remaining yellow oil is the pentaethyl ester of the title compound. For saponification, 150 ml of tetrahydrofuran an 150 ml (750 mmol) of 5 n sodium hydroxide solution arc added and allowed to stir for four hours at room temperature. The aqueous phase is separated, filtered several times on activated carbon and acidified with 50% by volume of sulfuric acid. It is allowed to stir for 24 hours in an ice bath, the precipitate is suctioned off, it is washed with ice water and dried in a vacuum at 50° C. 55.8 g (62% of theory) of the title compound is obtained as a white powder with a decomposition point above 250° C.

Analysis: C 46.69 H 5.09 N 10.89 (calculated) 46.48 5.20 11.01 (found)

d) 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-(hydroxyphenyl)-undecanedioic Acid

51.4 g (0.1 mol) of the compound obtained under c) is suspended in 500 ml of water and brought into solution by adding conc. sodium hydroxide solution. The solution is mixed in an autoclave with 5 g of palladium-carbon catalyst (10% Pd) and saturated with hydrogen gas. After completion of the hydrogenation, it is suctioned off from the catalyst, the solution is filtered on activated carbon and mixed with 15 ml of glacial acetic acid. Then, a solution of 11 g (150 mmol) of sodium nitrite in 50 ml of water and 50 ml of glacial acetic acid is simultaneously instilled in the ice bath with stirring, so that an inner temperature of 5° C. is not exceeded. It is allowed to stir for two hours at 5° C., then for two more hours at room temperature, 50 ml of nitric acid (1:3) is added by instillation and heated for three hours to 50° C. After cooling of and stirring in the ice bath overnight, the precipitate is suctioned off, washed with water and recrystallized from 90% ethanol. 29.1 g (60% of theory) of the title compound is obtained as a white powder with a decomposition point above 250° C.

Analysis: C 49.48 H 5.61 N 8.66 49.52 5.80 8.62

e) 3,6,9-Triaza-3,6,9-tris(carboxymethyl)-4-(4-ethoxyphenyl)-undecanedioic Acid

4.85 g (10 mmol) of the compound obtained under d) is dissolved in 20 ml of dimethyl formamide. After cooling off in the ice bath, 300 mg (10 mmol) of 80% sodium hydride and then 1.56 g (10 mmol) of iodine ethane are carefully added and allowed to stir at room temperature overnight. It is heated for two hours to 40° C., 5 ml of water is carefully instilled and the solution is evaporated to dryness in a vacuum. The residue is stirred up with 100 ml of diethyl ether overnight, suctioned off and suspended in 20 ml of 2 n hydrochloric acid. It is allowed to stir for one hour, again suctioned off, washed with water and dried in a vacuum at 40° C. [Several words illegible] title compound is obtained as a white powder with an uncharacteristic decomposition point.

Analysis: C 51 46 H 6.08 N 8.18 51.33 6.17 8.13

f) Disodium Salt of the Gadolinium Complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-ethoxyphenyl)-undecanedioic Acid

5.0 g of the compound obtained under e) is reacted in 30 ml of water with 1812 mg (5 mmol) of gadolinium oxide at 80° C. within one hour. The solution is ultrafiltered and freeze-dried. The title compound is obtained in quantitative yield with a gadolinium content of 22.1% (relative to the anhydrous substance).

Melting point: greater than 300° C.

EXAMPLE 12

Analogously, as described in example 11, starting from 2-amino-4-(4-nitrophenyl)-butyric acid, the complexes, according to the invention, of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-4-(4-ethoxyphenylethyl)-undecanedioic acid are obtained.

Melting point: greater than 300° C.

EXAMPLES FOR IN VIVO NMR DIAGNOSTICS

Example 1

Images were obtained at various times after administration of the disodium salt of the gadolinium complex of Example 1(c) to rats with the aid of an NMR tomograph by General Electric, specifically developed for animal experimental research.

Spin echo scans were made with the NMR tomograph (CSI 2 T) at 2 tesla (TR time of 400 ms and TE time of 20 ms). The layer thickness of this T_1-weighted imaging sequence was 3 mm; the image matrix was 128×128.

The contrast medium was administered intravenously into a caudal vein of a male hairless rat (Lew/Mol) weighing 190 g, in a dose of 0.06 mmol/kg The animal had a Brown Pearce tumor in the thigh and was anesthetized for the study by means of an intramuscular administration of "Ketavet"/"Rompun".

Various dark structures are visible in the abdomen in the coronary blank scan (baseline, No. 1). No differentiation was possible between intestinal lumen and stomach.

One minute after administration (No. 2), the first enhancement is already apparent in the urinary bladder. A strong increase in contrast is visible in the stomach 45 minutes after injection (No. 3). A good visualization of the tumor (at the level of the reference tube) of the urinary bladder, and of the stomach can be observed 60 minutes after injection (No. 4). Moreover, contrasting of the intestine can likewise be observed. This makes it possible to distinguish among intestinal loops, fat, as well as lymphatic nodes (lymphomas). Contrasting of the renal pelvis is also striking;

this image can be even more improved 65 minutes after injection in a somewhat different layer (No 5). 180 minutes after injection, the contrast enhancement is likewise clearly recognizable in an axial scan in the zone of the liver. This makes it possible to differentiate among the stomach, the liver, the duodenum, and the pancreas.

Example 2

The test animals were female rats of the strain Lew/Mol weighing 160–180 g. Prior to imaging, the animals were anesthetized ("Rompun"+"Ketavet") and provided with a catheter in the caudal vein to administer the contrast medium. Imaging took place in an MRI experimental device by General Electric (field strength 2 tesla). First of all, the images (7, 9, 11) were made without contrast medium with a T_1-weighted spin echo sequence (TR=400 msec, TE=20 msec, axial section plane, layer thickness 3 mm). The liver appears in each case with the normal signal intensity; the stomach is darker in tendency than the liver. In case of animal 1, the stomach exhibits, in part, a rather high signal intensity. This is due to feed residues, the feed containing manganese in relatively high concentrations (at the time of the test, the animals had been fasting for 6 hours) . Animal 3 had been implanted with an osteogenic sarcoma three weeks previously; this sarcoma was of equal contrast in the blank image and could not be defined. The administration of contrast medium took place via the venous catheter with a dose of 0.1 mmol Gd/kg (concentration of the solutions 0.05 mmol Gd/ml in 0.9% NaCl) for all 3 compounds.

A marked enhancement of the liver can be found for all 3 compounds after 90 minutes [Example 8(c)] and, respectively, after 60 minutes have elapsed upon administration [Example 9(c); FIG. 12, Example 10(c)]; this is due to uptake by the hepatocytes and cannot be observed at this point in time after administration with the contrast medium for NMR tomography, "Magnevist", heretofore the sole contrast medium available on the market. In case of animal 3 [Example 10(c)], the tumor is now additionally clearly visible, which has not absorbed the contrast medium at all, or only to a lesser proportion.

Furthermore, all compounds—most strongly in case of Example 10(c), least in case of Example 8(c)—show great enhancement of the stomch. This offers additional diagnostic possibilities in view of an improved distinction of liver and stomach.

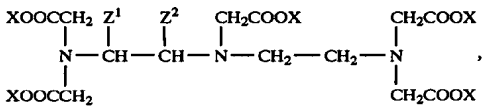
The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

What is claimed is:

1. A method of enhancing an NMR image comprising administering to a patient a compound of the formula

(I)



wherein

one of Z^1 and Z^2 is H and the other is

$$—(CH_2)_m—(C_6H_4)_q—(O)_k—(CH_2)_n—(C_6H_4)_l—(O)_r—R,$$

wherein

m and n, independently, are each 0–20,

k, l, q and r are each, independently, 0 or 1,

R is H, C_1–C_6-alkyl, OR^1-substituted C_1–C_6-alkyl or CH_2COOR^1,

R^1 is H, C_1–C_6-alkyl or benzyl; and

X is, in each case, a hydrogen atom or a metal ion equivalent of an element of atomic number 21–29, 42, 44 or 58–70;

with the provisos that:

at least two X groups represent a metal ion equivalent of atomic number 21–29, 42, 44 or 58–70;

when n and l are each 0, then k and r are not each simultaneously 1;

$—(O)_r—R$ is not —OH;

Z^1 and Z^2 are not $—C_6H_5$, $—CH_2—C_6H_5$, $—CH_2—C_6H_4—O—CH_2—COOCH_2C_6H_5$ or $—CH_2—C_6H_4—O—(CH_2)_5—COOCH_2C_6H_5$; and

at least one of q and l is 1;

or a physiologically acceptable salt thereof with an inorganic and/or organic base, an amino acid or an amino acid amide.

2. A method of claim 1, wherein Z^1 is hydrogen and Z^2 is $—(CH_2)_m—(C_6H_4)_q—(O)_k—(CH_2)_n—(C_6H_4)_l—(O)_r—R$, which is not hydrogen.

3. A method of claim 1, wherein Z^2 is hydrogen and Z^1 is $—(CH_2)_m—(C_6H_4)_q—(O)_k—(CH_2)_n—(C_6H_4)_l—(O)_r—R$, which is not hydrogen.

4. A method of claim 1, wherein Z^1 is $—CH_2—C_6H_4—OCH_3$, $—CH_2—C_6H_4—O—CH_2—C_6H_4—OCH_3$, $—CH_2—O—CH_2—C_6H_5$, $—CH_2—C_6H_4—O—CH_2—COOH$, $—CH_2—C_6H_4—OC_2H_5$, $—CH_2—C_6H_4—OC_4H_9$ or $—CH_2—C_6H_4—O—CH_2—C_6H_5$.

5. A method of claim 4, wherein Z^1 is $—CH_2—C_6H_4—OCH_3$, $—CH_2—C_6H_4—O—CH_2—C_6H_4—OCH_3$, $—CH_2—O—CH_2—C_6H_5$ or $—CH_2—C_6H_4—O—CH_2—COOH$.

6. A method of claim 1, wherein Z^2 is $—CH_2—C_6H_4—OCH_3$, $—CH_2—C_6H_4—O—CH_2—C_6H_4—OCH_3$, $—CH_2—O—CH_2—C_6H_5$, $—CH_2—C_6H_4—O—CH_2—COOH$, $—CH_2—C_6H_4—OC_2H_5$, $—CH_2—C_6H_4—OC_4H_9$ or $—CH_2—C_6H_4—O—CH_2—C_6H_5$.

7. A method of claim 6, wherein Z^2 is $—CH_2—C_6H_4—OCH_3$, $—CH_2—C_6H_4—O—CH_2—C_6H_4—OCH_3$, $—CH_2—O—CH_2—C_6H_5$ or $—CH_2—C_6H_4—O—CH_2—COOH$.

8. A method of claim 1, wherein at least three X groups represent a Gd ion.

9. A method of claim 4, wherein at least three X groups represent a Gd ion.

10. A method of claim 6, wherein at least three X groups represent a Gd ion.

11. A method of claim 1, wherein said compound is:

gadolinium complex of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-4-(4-methoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

europium complex of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-4-(4-methoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

iron(III) complex of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-4-(4-methoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

gadolinium complex of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-5-(4-methoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

gadolinium complex of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-4-[4-(4-methoxybenzyloxy)benzyl] undecanedioic acid or a physiologically acceptable salt thereof;

gadolinium complex of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-4-benzyloxymethylundecanedioic acid or a physiologically acceptable salt thereof;

gadolinium complex of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-4-(4-carboxymethoxybenzyl) undecanedioic acid or a physiologically acceptable salt thereof;

gadolinium complex of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-4-(4-ethoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

europium complex of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-4-(4-ethoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof,

iron complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-ethoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

gadolinium complex of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-4-(4-butoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

europium complex of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-4-(4-butoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

iron complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)4-(4-butoxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof,

gadolinium complex of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-4-(4-benzyloxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

europium complex of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-4-(4-benzyloxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof;

iron complex of 3,6,9-triaza-3,6,9-tris(carboxymethyl)-4-(4-benzyloxybenzyl)undecanedioic acid or a physiologically acceptable salt thereof.

12. A method of claim 1, wherein the renal system is imaged.

13. A method of claim 1 wherein the hepatobiliary system is imaged.

14. A method according to claim 1, wherein two of the X groups represent manganese(II), iron(II), cobalt(II) or copper(II); or three of the X groups represent chromium(III), praseodymium(III), neodymium(III), samarium(III), ytterbium(III), gadolinium(III), terbium(III), dysprosium (III), holmium(III), erbium(III), or iron(III).

15. A method to claim 1, wherein Z^1 is $—C_6H_4—O—C_2H_5$ or $—C_2H_4—C_6H_4—O—C_2H_5$.

16. A method according to claim 1, wherein said compound is gadolinium complex of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-4-(4-ethoxyphenyl)undecanedioic acid or a physiologically acceptable salt thereof.

17. A method according to claim 1, wherein said compound is a complex of 3,6,9-triaza-3,6,9-tris (carboxymethyl)-4-(4-ethoxyphenylethyl)undecanedioic acid and a metal ion of atomic number 21–29, 42, 44 or 57–83, or a physiologically acceptable salt thereof.

18. A method according to claim 1, wherein R is C_{1-6}-alkyl or C_{1-6}-alkyl substituted by $—OR^1$.

19. A method according to claim 1, wherein one of Z^1 and Z^2 is $—CH_2—C_6H_4—O—(CH_2)_n—(C_6H_4)_l—(O)_r—R$.

20. A method according to claim 1, wherein one of Z^1 and Z^2 is $—(CH_2)—C_6H_4—O—CH_2—C_6H_4—(O)_r—R$.

21. A method according to claim 1, wherein the X groups which do not represent a metal ion equivalent of atomic number 21–29, 42, 44 or 57–83 are individually lithium, potassium or sodium, or two such X groups are calcium or magnesium.

22. A method according to claim 1, wherein X groups which are not a metal ion equivalent of an element of atomic number 21–29, 42, 44 or 57–83 represent a salt with ethanolamine, diethanolamine, morpholine, glucamine, N,N-dimethylglucamine, N-methylglucamine, lysine, arginine, ornithine, lysine methylamide, glycine ethylamide or serine methylamide.

23. A method according to claim 11, wherein Z^2 is $—C_6H_4—OC_2H_5$ or $—C_2H_4—C_6H_5—OC_2H_5$.

24. A method according to claim 1, wherein said compound is administered in a dose of 1 μmole/kg–5 mmole/kg.

25. A method according to claim 24, wherein the dose of said compound is 10 μmole/kg–0.5 mmole/kg.

26. A method according to claim 1, wherein said compound is administered by intravenous injection.

27. A method according to claim 1, wherein said compound is administered orally.

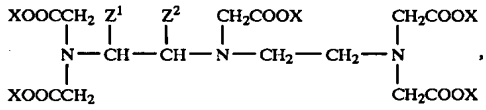
28. A method according to claim 1, wherein at least one of k and r is 1.

29. A method according to claim 1, wherein said compound is administered as a pharmaceutical composition comprising said compound and a pharmaceutically acceptable carrier.

30. A method according to claim 1, wherein R^1 is H or C_1–C_6-alkyl.

31. A method of enhancing an NMR image of the GI tract of a patient comprising administering a compound of the formula

(I)



wherein

one of Z^1 and Z^2 is H and the other is

$$—(CH_2)_m—(C_6H_4)_l—(O)_k—(CH_2)_n—(C_6H_4)_l—(O)_r—R,$$

wherein

m and n independently are 0–20,

k, l, q and r each independently is 0 or 1,

R is hydrogen, optionally OR^1-substituted C_1–C_6-alkyl or CH_2COOR^1,

R^1 is hydrogen, C_1–C_6-alkyl or benzyl, and

X is, in each case, a hydrogen atom or a metal ion equivalent of an element of atomic number 21–29, 42, 44 or 58–70,

with the provisos that:

at least two of the substituents X represent a metal ion equivalent of atomic number 21–29. 42, 44 or 58–70; and

when n and l are each 0, then k and r are not each simultaneously 1;

$-(O)_r-R$ is not —OH;

Z^1 and Z^2 are not $-C_6H_5$, $-CH_2-C_6H_5$, $-CH_2-C_6H_4-O-CH_2-COOCH_2C_6H_5$ or $-CH_2-C_6H_4-O-(CH_2)_5-COOCH_2C_6H_5$; and

at least one of q and l is 1;

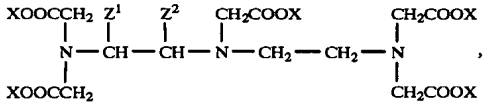
or a physiologically acceptable salt thereof with an inorganic and/or organic base, an amino acid or an amino acid amide.

32. A method according to claim **31**, wherein said compound is administered as a pharmaceutical composition comprising said compound and a pharmaceutically acceptable carrier.

33. A method according to claim **31**, wherein R^1 is H or C_1–C_6-alkyl.

34. A method of enhancing NMR imaging of a patient having renal insufficiency comprising administering to a patient a compound of the formula

(I)



wherein

one of Z^1 and Z^2 is H and the other is $-(CH_2)_m-(C_6H_4)_q-(O)_k-(CH_2)_n-(C_6H_4)_l-(O)_r-R$,

wherein

m and n, independently, are each 0–20,

k, l, q and r are each, independently, 0 or 1,

R is H, C_1–C_6-alkyl, OR^1-substituted C_1–C_6-alkyl or CH_2COOR^1,

R^1 is H, C_1–C_6-alkyl or benzyl; and

X is, in each case, a hydrogen atom or a metal ion equivalent of an element of atomic number 21–29, 42, 44 or 58–70;

with the provisos that:

at least two X groups represent a metal ion equivalent of atomic number 21–29, 42, 44 or 58–70;

when n and l are each 0, then k and r are not each simultaneously 1;

$-(O)_r-R$ is not —OH;

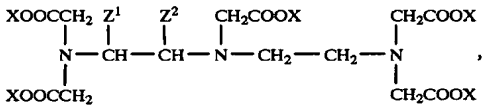
Z^1 and Z^2 are not $-C_6H_5$, $-CH_2-C_6H_5$, $-CH_2-C_6H_4-O-CH_2-COOCH_2C_6H_5$ or $-CH_2-C_6H_4-O-(CH_2)_5-COOCH_2C_6H_5$; and

at least one of q and l is 1;

or a physiologically acceptable salt thereof with an inorganic and/or organic base, an amino acid or an amino acid amide.

35. In a method of NMR imaging a patient comprising administering an NMR contrast agent to said patient, the improvement wherein said contrast agent is a compound of the formula

(I)



wherein

one of Z^1 and Z^2 is H and the other is $-(CH_2)_m-(C_6H_4)_q-(O)_k-(CH_2)_n-(C_6H_4)_l-(O)_r-R$,

wherein

m and n, independently, are each 0–20,

k, l, q and r are each, independently, 0 or 1,

R is H, C_1–C_6-alkyl, OR^1-substituted C_1–C_6-alkyl or CH_2COOR^1,

R^1 is H, C_1–C_6-alkyl or benzyl; and

X is, in each case, a hydrogen atom or a metal ion equivalent of an element of atomic number 21–29, 42, 44 or 58–70;

with the provisos that:

at least two X groups represent a metal ion equivalent of atomic number 21–29, 42, 44 or 58–70;

when n and l are each 0, then k and r are not each simultaneously 1;

$-(O)_r-R$ is not —OH;

Z^1 and Z^2 are not $-C_6H_5$, $-CH_2-C_6H_5$, $-CH_2-C_6H_4-O-CH_2-COOCH_2C_6H_5$ or $-CH_2-C_6H_4-O-(CH_2)_5-COOCH_2C_6H_5$; and

at least one of q and l is 1;

or a physiologically acceptable salt thereof with an inorganic and/or organic base, an amino acid or an amino acid amide.

* * * * *

ATTACHMENT B

1. **Certificate of Correction issued April 9, 2002 with regards to US Patent No. 6,039,931**

2. **Maintenance Fee Statement for payment of 4th year annuity for US Patent No. 6,039,931 on August 22, 2003**

3 **Maintenance Fee Statement for payment of 8h year annuity for US Patent No. 6,039,931 on August 21, 2007**

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 6,039,931
DATED : March 21, 2000
INVENTOR(S) : Schmitt-Williams et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 22, claim 20,
Line 2, reads "(CH_2)" should read -- $(CH_2)_m$ --

Signed and Sealed this

Ninth Day of April, 2002

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Customer Number: 225

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PATENT NUMBER	FEE AMT	SUR-CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	SI EN
6,039,931	$890.00	$0.00	08/22/03	08/319,357	03/21/00	10/06/94	04	

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PATENT NUMBER	FEE AMT	SUR-CHARGE	PYMT DATE	U.S. APPLICATION NUMBER	PATENT ISSUE DATE	APPL. FILING DATE	PAYMENT YEAR	E
6,039,931	$2,300.00	$0.00	08/21/07	08/319,357	03/21/00	10/06/94	08	

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ATTACHMENT C

1. **IND 54875 Updated Regulatory History Summary (November 2000 – December 2006)**

2. **Eovist – Liver Lesion Characterization History (12/19/97 to 2/13/01)**

3. **IND 54875 Chron Log (2/6/06 to 7/1/08)**

4. **List of Submissions for NDA 22-090 (6/29/07 to 10/11/07)**

5. **NDA Chron Log (3/2/07 to 1/14/08)**

6. **NDA Chron Log (4/7/08 to 8/4/08)**

7. **IND 54875 Submissions Log (2/5/05 to 2/7/08)**

8. **FDA Approval Letter dated July 3, 2008 (acknowledgement of receipt of submissions in second paragraph)**

Gadolinium EOB-DTPA Injection - [PRIMOVIST® Injection, formerly EOVIST™ Injection] - IND 54,875

Regulatory history summary (November 2000 to Oct 2006)

Division's communications /Date	Berlex's communications /Date[1]	Response to/ reference to	Actions	Comments[2]
			Type C Meeting, Nov 16, 2000	Discussion of the revised indication for Primovist® Injection: "Eovist™ (gadolinium EOB DTPA) Injection is a contrast agent for Magnetic Resonance Imaging (MRI) of the liver in adult patients using T-1 weighted sequences. It is administered as an intravenous bolus injection. Eovist™ Injection provides additional information compared with pre-contrast images alone about the morphologic and enhancement patterns of liver lesions resulting in improved lesion characterization. Enhancement of liver parenchyma provides additional information about the number, size and segmental distribution of liver lesions, thereby improving liver lesion detection. Excretion of Eovist™ Injection provides information about biliary structures." Confirmation sought that the Phase 3 clinical development program as planned can support the revised proposed indication.
	Serial No. 031/	Reference to		Change in protocol 014763 (Amendment #1, special

[1] Serial No. 35, 39, 41, 42 and 46 are Annual Reports of the years 2000 – 2005

[2] In case of "changes in protocol" only significant changes are given in this table

Division's communications /Date	Berlex's communications /Date[1]	Response to/ reference to	Actions	Comments[2]
	Dec 5, 2000	Serial No. 021 (Draft Protocol 014763, US characterization study)		population study).
	Serial No. 032/ Dec 8, 2000	Response to the Division's pharmacology/toxicology comments received by fax on July 3, 2000/ Reference to Serial Nos. 014, 017 and 023		Responses to comments on - 4-week systemic toxicology study of ZK 13984 in rats, - 4-week systemic toxicology study of ZK 13984 in dogs, - cardiovascular safety study in a non rodent species. Submission of the draft protocol for a cardiovascular safety study in dogs
	Serial No. 033/ Dec 18, 2000	Reference to Type C meeting held on November 16, 2000		Submission of the presentation slides. Submission of detailed description of the Blinded Read procedure (protocol 303308) Request follow-up meeting along with questions.
	Serial No. 034/ Jan 5, 2001	Reference to Serial No. 030 (Draft Protocol 014468)		Change in protocol 014468 (amendment #1, special population study).
Fax/ Jan 9, 2001		Response to the specific questions raised by Berlex during the Type C meeting on November 16, 2000 / Reference to Type C Meeting package [Serial No. 028]		Written response to specific questions; Further comments regarding safety and efficacy
	Fax / Feb 7, 2001:			General question regarding the participation of a sub-investigator from the US characterization study as a blinded reader for the EU characterization study.
Fax / Feb 13, 2001		Reference to Serial Nos. 028, 031 and 034		Medical reviewer's comments (draft) on - revised protocol 014763 (September 12, 2000, US characterization study) - revised protocol 014468 (September 26, 2000, special

Division's communications /Date	Berlex's communications /Date[1]	Response to/ reference to	Actions	Comments[2]
				population study) - Protocol 303308 (August 8, 2000, US characterization study, Blinded Read)
Fax / May 1, 2001		Response in lieu of Teleconference (scheduled for February 8, 2001)/ Reference to Serial No. 033 (Request for follow up meeting)/ Reference to Type C meeting on Nov 16, 2000		Response to the questions submitted with Serial No 033 (Request for follow up meeting). Final minutes of the Type C meeting held on Nov 16, 2000.
	Serial No. 036/ May 7, 2001	Reference to Serial No. 030 (Draft Protocol 014468) Serial No. 034 (Amendment # 1 to Protocol 014468) Serial No. 021 (Draft Protocol 014763) Serial No. 031 (Amendment # 1 to Protocol 014763)		Change in protocol No. 014468 (Amendment # 2, special population study) Significant change: addition of two study groups: Group 8, healthy elderly (≥ 65 years of age; 3 males and 3 females) and Group 9, Change in protocol No. 014763 (Amendment # 2, US characterization study).
	Serial No. 037 / Sep 7, 2001	Reference to Serial No. 030 (Draft Protocol 014468) Serial No. 034 (Amendment # 1 to Protocol 014468) Serial No. 036 (Amendment # 2 to Protocol 014468) Serial No. 021(Draft Protocol 014763 Serial No. 031 (Amendment # 1 to Protocol 014763)		Change in protocol 014468 (Amendment # 3, special population study) Change in protocol 014763 (Amendment # 3, US characterization study).

Division's communications /Date	Berlex's communications /Date[1]	Response to/ reference to	Actions	Comments[2]
		Serial No. 036 (Amendment # 2 to Protocol 014763)		
	Serial No. 040/ Feb 5, 2004			Submission of final clinical study reports for the following studies completed in 2002: Clinical Study Report No. A03779 (Protocol 97160 US detection study) Clinical Study Report No. A01908 (Protocol 014763, US characterization study) Clinical Study Report No. A04410 (Protocol 014468, special population study)
	Serial No. 043/ Oct 14, 2005			Request for Type C Meeting to discuss the results, the significance and the limitations of a prediction model for liver lesion characterization
	Serial No. 044/ Dec 15, 2005	Reference to Serial No. 043 (Request for Type C Meeting)		Sponsor package for Type C Meeting scheduled for January 19, 2006, containing the report on the evaluation of the prediction model and the Clinical Study Report of the new Blinded Reader Study (Protocol No. 305578), and the synopses of the 4 pivotal clinical phase 3 studies.
Fax / Jan 18, 2006		Response to the pre-meeting package submitted with Serial No. 044		Comments on the results of the prediction model for liver lesion characterization; Comments and information request on design and results of the 4 pivotal clinical phase 3 studies.
		Type C Meeting scheduled for Jan 19, 2006 was cancelled	T-con Jan 19, 2006	Discussion of comments received on January 18, 2006. Agreement on "end of phase 3 meeting" (Type C Meeting) to be scheduled in April 2006, with meeting request to be sent out in early February. Pre-meeting package to contain responses to the information requests received with the FDA Fax dated January 18, 2006, study reports for all four pivotal studies,

Division's communications /Date	Berlex's communications /Date[1]	Response to/ reference to	Actions	Comments[2]
				summary information on CMC and preclinical development.
Letter / Jan 30, 2006		T-con on Jan 19, 2006		Official minutes of the T-con held on Jan 19, 2006
	Serial No. 045/ Feb 8, 2006	Comments received with FDA Fax dated January 18, 2006; T-con held with the Division on Jan 19, 2006		Request for Type C Meeting to present and discuss the results of the development of Primovist with focus on the clinical development.
	Serial No. 047[33] Mar 20, 2006			Sponsor package for Type C Meeting scheduled for April 20, 2006, containing the response to the comments received with the Division's Fax dated Jan 18, 2006, brief summaries of clinical, preclinical and CMC development of Primovist, and the full study reports of the 4 pivotal studies in electronical form.
Fax / Apr 17, 2006		Reference to Serial No. 047[3]		Comments for CMC in preparation of Type C Meeting scheduled for Apr 20, 2006
Fax / Apr 18, 2006		Reference to Serial No. 047[3]		Comments and information requests on clinical topics in preparation of Type C Meeting scheduled for Apr 20, 2006. For completeness, the CMC comments from Apr 17, 2006 were sent again with this fax.
	Fax / Apr 19, 2006	CMC comments received by Fax on Apr 17, 2006		Response to CMC comments received from the Division on April 17, 2006
			Type C Meeting (end of	Discussion of the clinical development of Primovist with special focus on the clinical comments received from the Division on April 18, 2006 and the positioning of

[3] This Serial was numbered erroneously 046 in the first place; with Serial No 048 Berlex has requested to correct the Serial number

Division's communications /Date	Berlex's communications /Date[1]	Response to/ reference to	Actions	Comments[2]
			phase 3 meeting) Apr 20, 2006	Primovist. Discussion of the CMC comments received from the Division on April 17, 2006. Agreement that Berlex submits a written response to the clinical comments received from the Division on April 18, 2006
Letter / May 11, 2006		Type C Meeting held on Apr 20, 2006		Official meeting minutes
	Serial No 49/ May 30, 2006	Official minutes of Type C meeting held on Apr 20, 2006		Comments on official meeting minutes received on May 16, 2006.
	Serial No 50/ June 16, 2006	Clinical comments received with Fax dated Apr 18, 2006; Type C meeting held on Apr 20, 2006		Written response to clinical comments received with Fax dated Apr 18, 2006, including Berlex' view on the positioning of Primovist
Fax / Sep 20, 2006		Serial No. 50		Clinical and statistical comments following the review of Serial No. 50
	Fax / Sep 29, 2006	Clinical and statistical comments received with fax dated Sep 20, 2006		Confirmation that Berlex has no further questions on the clinical and statistical comments received with fax dated Sep 20, 2006. Information that Berlex will submit Pre-NDA meeting request as next formal step.
	Serial 51/ Oct 27, 2006	Serial No 044 and 047, Berlex' fax dated Sep 29, 2006		Request for Pre-NDA meeting to acquaint the reviewers to content, presentation and format of the NDA for Primovist and to discuss specific questions prior to the NDA submission
Letter dated Nov 13, 2006		Serial No 51		Request for pre-NDA meeting denied as premature due to the need of clarification of Pharm/Tox and CMC issues prior to establishing the pre-NDA meeting
Letter dated Nov 14 2006				Request for quarterly update on information about association between Gd containing contrast agents and

Division's communications /Date	Berlex's communications /Date[1]	Response to/ reference to	Actions	Comments[2]
				Nephrogenic Systemic Fibrosis or Nephrogenic Fibrosing Dermopathy (NSF/NFD)
	FAX / Nov 15, 2006	FDA Letter dated 13 Nov 2006		Request for T-con with Pharm/Tox Review Team and the CMC Review Team
FAX / Nov 16, 2006		Serial No 51		Pharmacology/Toxicology comments
	Serial No 52 / Nov 21, 2006	FDA FAX from Nov 16, 2006		Written response to Pharm/Tox commenst received 16 Nov 2006, including overview tables of pharmacology and toxicology studies conducted with Primovist as requested
	Serial No 53 / Dec 1, 2006	FDA Letter dated Nov 14, 2006		First submission of update on Nephrogenic Systemic Fibrosis or Nephrogenic Fibrosing Dermopathy (NSF/NFD) in association with Primovist (no cases reported), as requested.
FAX / Dec 14, 2006		Serial No 051 (pre-NDA meeting request)		FDA participants in Dec 14, 2006 teleconference, CMC information request, CMC and Pharmacology/Toxicology comments to questions submitted with pre-NDA meeting request (Serial No 051)
		Berlex Fax dated Nov 15, 2006 (meeting request), Serial No 051, FDA Fax dated Dec 14, 2006	T-con / Dec 14, 2006	Discussion of CMC and nonclinical issues
	FAX / Dec 18, 2006	CMC information request (FDA FAX dated Dec 14, 2006)		CMC overview tables Primovist stability studies

[1]Serial No. 35, 39, 41, 42 and 46 are Annual Reports of the years 2000 – 2005
[2] In case of "changes in protocol" only significant changes are given in this table

Eovist – Liver Lesion Characterization History

12/19/97	Original IND Submission	Original IND Submission
3/20/98	Letter (003)*	Response to the Division's 3/11/98 comments on the clinical development plan and the detection protocol. One comment refers to characterization. "Please clarify the characteristics of a lesion which result in it being judged as benign or malignant. These criteria should ideally be established prior to Phase 3 investigators."
3/26/98	Meeting*	A meeting was held to discuss the clinical development plan and the detection protocol. Dr. Love commented on the proposed lesion characterization diagnostic algorithm/probability model.
3/31/98	Fax*	Sent diagnostic algorithm slides presented during 3/26/98 meeting in preparation for 4/2/98 T-con.
4/1/98	Call*	Request to schedule date to discuss diagnostic algorithm with Dr. Arnstein.
4/2/98	T-Con*	T-Con to clarify the probability model of lesion characterization
6/18/98	Letter (005)*	Letter of understanding for 3/26/98 meeting and 4/2/98 T-con. Includes summary of lesion characterization diagnostic algorithm/probability model.
6/3/99	Letter (012)*	Response to 10/19/98 clinical comments on the detection protocol. Comment 1 deals with characterization is referenced in the 2/3/00 T-con.
9/17/99	Letter	Draft Protocol ME014763 for Phase 3 characterization study submitted to FDA, comments requested.
12/22/99	Letter	Year-end summary letter to FDA reminds Division that comments on the characterization protocol have not been received.
1/5/00	Fax	Comments on characterization protocol received from FDA.
2/3/00	T-Con*	T-Con with FDA scheduled in response to our year-end summary of outstanding issues. Regarding characterization, Dr. Jones' comments indicate continuing confusion about this part of the indication.
4/13/00	Letter (021)*	Final characterization protocol submitted along

		with responses to FDA's 1/5/00 comments; clarified characterization claim; revised indication; requested meeting if FDA felt need to discuss new indication.
		Hold on meeting request until after June Berlex-SAG meeting.
5/1/00	Fax from FDA	Comments regarding 033 and meeting minutes from November 16, 2000.
6/9/00	Berlex-SAG meeting in US	Conclusion: Request meeting with FDA. Plan is still to defend current indication and studies. Blinded reader protocol for characterization study must be submitted to FDA for the Division to comment on the characterization indication. No algorithm will be developed.
July 2000	Plan ???	Letter requesting meeting circulated – Submit draft blinded reader protocol for the characterization study to FDA and request meeting to determine acceptability of the characterization part of the indication. ON HOLD BY DR. BALZER.
8/25/00	Meeting Request (028)	Containing draft protocol Blinded reader – study characterization – 303308.
11/16/00		Meeting took place.
12/18/00	Request T-con (033)	Revised Protocol Clinical Study.
1/9/01	Fax from FDA	Commented to slides presented at meeting on November 16th.
2/13/01	Fax from FDA	Comments: 028 Draft Protocol Blinded reader: characterization: 303308 031 Revised Protocol Cl. Dev. Us =A4752 034 Revised Protocol Special Population 14468 (8/26/00)

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DATE SUBMITTED	DESCRIPTION	SERIAL NO.
July 1, 2008	IND Safety Report-15-day Follow-up	078
June 23, 2008	IND Safety Report-15-day Follow-up	077
June 23, 2008	IND Safety Report-15-day Initial	076
June 16, 2008	IND Safety Report-15-day Initial and 15-day Follow-up	075
June 2, 2008	NSF Quarterly Safety Update Report.	074
May 21, 2008	IND Safety Report-	073
April 24, 2008	IND Safety Report. 15 day Initial report	072
March 31, 2008	IND Safety Report. 15 day Initial report	071
Feb. 29, 2008	Quarterly Safety Update on NSF	070
Feb. 18, 2008	Annual Report. 2007	069
Feb. 7, 2008	IND Safety Report.. Follow-up #1	068
Jan. 28, 2008	Initial 15-day – IND Safety Reports for 200811398GPV and 200811248 GPV.	067
Jan. 14, 2008	IND Safety Report-15-day follow-up including MedWatch form and faxed copy to FDA.	066
Jan. 3, 2008	IND Safety Report 15-day Initial report	065
Dec. 7, 2007	NSF Quarterly Safety Update Report.	064
Sept. 5, 2007	NSF Quarterly Safety Update Report	063
July 18, 2007	Risk management plan for Primovist. T. Brown will respond with rationale for	
June 28, 2007	Submission of Primovist NDA	
June 20, 2007	Discussion of dates for Applicant Orientation Meeting.	
June 18, 2007	Informed FDA of intent to submit Primovist NDA on June 29, 2007.	
June 1, 2007	NSF Safety Update Report	062
May 22, 2007	Previous submission (SN061) was distributed, with our response to FDA comments received on May 4, 2007, to statistical and clinical reviewers. They accepted our response and have no further comments or open issues.	
May 16, 2007	T. Brown confirmed receipt of written response to statistical comments received on May 4, 2007.	
May 15, 2007	Submission of response to written comments. Form	061

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May 1, 2007	Written response to comments received April 13, 2007	060
April 18, 2007	Response to written comments being prepared. Also when to expect NDA submission and questions about meeting minutes	
April 13, 2007	Comments from statisticians re pre-NDA meeting minutes.	
April 4, 2007	Comments to official pre-NDA meeting minutes received.	
Mar. 28, 2007	Sponsor's comments on FDA Pre-NDA meeting minutes.	059
Mar. 28, 2007	Sponsor's comments on official pre-NDA meeting minutes.	
Mar. 28, 2007	Confirming participants at eCTD demonstration. Also comments on pre-NDA meeting minutes.	
Mar. 14, 2007	Demonstration of Primovist eCTD linking strategy.	
Mar. 14, 2007	Final list of participants for Primovist eCTD demonstration without P. Mayer	
Mar. 1, 2007	Letter explaining monitoring of safety and providing safety updates according to regulations.	058
Feb. 16, 2007	Annual Report 2006	057
Feb. 14, 2007	List of attendees for pre-NDA meeting.	
Feb. 5, 2007	FDA information re FDA participants in pre-NDA meeting.	
Jan. 11, 2007	Information re company name change from Berlex, Inc. to Bayer Healthcare Pharmaceuticals, Inc.	056
Feb. 6, 2006	Annual report. 2005.	046

Submissions to NDA 22-090 Primovist Injection

eCTD Serial No	Content	Submitted by	Date
0000	Original NDA submission	S Jennings	29 Jun 2007
	Exchange DVD	S Jennings	20 Jul 2007
0001	First set of additional datasets	S Fehr	13 Aug 2007
0002	Notification that name objection will be rebutted	S Fehr	13 Aug 2007
0003	Second set of additional datasets	S Jennings	17 Aug 2007
0004	Slides presented at the Applicant Orientation Meeting	S Jennings	21 Aug 2007
0005	Clinical summary tables	S Jennings	05 Sep 2007
0006	NSF quarterly update	S Jennings	05 Sep 2007
0007	Replacement Module 5	S Jennings	27 Se 2007
0008	Response to Microbiology (filing letter)	S Jennings	11 Oct 2007
0009	Response to CMC (filing letter	S Jennings	11 Oct 2007

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Jan. 14, 2008	Primo_Lesion_Tables_ 12_07, T con Meeting Minutes held 12/17/07, Listings for Detection Studies, and Listings for Characterization	eCTD 0021
Jan. 14, 2008	Site specific information and Investigator Site contact sheet sent to Div. Scientific Investigations.	eCTD 0020
Jan. 14, 2008	Site specific information and Investigator Site contact sheet sent to Div. Medical Imaging and Hematology Products, HFD-160.	eCTD 0020
Jan. 11, 2008	Statistics documents (Primo_Lesion_Tables_12_07, T con Meeting Minutes held 12/17/07, Listings for Detection Studies, and Listings for Characterization Studies)	eCTD 0019
Jan. 9, 2008	All deliverables discussed at Dec. 17 T Con on target. Site specific info requested by K. Storm to be submitted on Jan. 14, 2008.	
Jan. 8, 2008	Requesting site-specific information on 5 clinical trial sites. Submission date to be early January.	
Jan. 7, 2008	Statistics documents (Primo_Lesion_Tables_12_07, T con Meeting Minutes held 12/17/07, Listings for Detection Studies, and Listings for Characterization Studies) sent to Div. Medical Imaging & Hematology Products, HFD-160	eCTD 0019
Jan. 2, 2008	Primo_Lesion_Tables_12_07 and meeting minutes from Dec. 17, 2007 T Con.	eCTD 018
Dec. 21, 2007	Contact information for two foreign investigators and the site specific information for 5 sites.	
Dec. 18, 2007	Change of contact for Primovist from James Hoover to Ayse Baker.	eCTD 0017
Dec. 17, 2007	Retention Justification for Primovist.	eCTD 0016
Dec. 14, 2007	Submitting Risk management Plan and Proposed NSF Protocol Outline.	eCTD 0015
Dec. 10, 2007	Quarterly Safety Update Report on NSF	eCTD 0013
Dec. 6, 2007	Response to FDA's CMC Information Request- Information requested re: DMF 20 414 for EOP-DTPA.	eCTD 014
September 5, 2007	Quarterly Safety Update Report on NSF	eCTD 0006
July 20, 2007	Replacement DVD for NDA 22-090. Revised so all files can be read.	
July 20, 2007	Technical difficulties with Primovist NDA submission.	
July 20, 2007	Replacement DVD sent via UPS today.	
July 18, 2007	Clarification of planned timelines for submission of risk management plan.	
July 12, 2007	Acknowledgement of receipt of NDA 22-090 Primovist Injection. Acknowledgement of receipt of waiver request.	
July 12, 2007	Receipt of NDA acknowledged. Application will be filed on August 31, 2007	

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July 3, 2007	NDA 22-090 has been sent to CDER, Office of Oncology Drug Products, Division of medical Imaging and Hematology Products NDA 22-090 is electronic submission in eCTD format.	
June 29, 2007	NDA 22-090 sent out via UPS today.	
June 29, 2007	Copy of Cover Letter for Original Application with all Also letter to R.D. Rieves re Original New Drug Application Also Statement of Certification, Prescription Drug User Fee Cover Sheet, Debarment of Certification, Form 3454, Form 3542a.	
April 25, 2007	Invoice from Pharmaceutics, LLC to Berlex. For Primovist Highlights Data Elements creation. Total: $1252.15. Approved by Patricia Mayer.	
March 9, 2007	Invoice from Kishor A. Dandekar, PHD for consulting services in preparation of ClinPharm Section of Primovist US-CTD.	
March 2, 2007	Meeting on Primovist on March 7, 2007 Briefing package.	

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April 2008-

DATE SUBMITTED	DESCRIPTION	SERIAL NO.
August 4, 2008 July 28, 2008 (doc date)	Request for advisory comments on Eovist promotional launch materials (product monograph and visual aid) submitted on July 29, 2008	
July 30, 2008	Submission of new contact person for NDA 22,090-Madhu Anant	eCTD 0044
July 17, 2008	CMC-changes being effected-supplement to add 2 alternate secondary packagers	eCTD 0043
July 17, 2008	Submission of EOVIST Approved Labeling to FDA	eCTD 0042
July 7, 2008	Notification of **APPROVAL** of Eovist NDA	
July 2, 2008	Submit responses in eCTD format to comments received via fax on June 26. Submitted to J. Moore via email on June 27.	eCTD 0041
July 1, 2008	Inquiry re status of pending NDA 22,090	
June 30, 2008	Bayer is required to do pediatric assessment for pending NDA 22,090.	
June 27, 2008	Response to FDA comments regarding revisions to Eovist labeling.	
June 26, 2008	Phone call from D. Rieves: Two items on the status of the NDA 22,090 under FDA review.	
June 25, 2008	Phone call from James Moore. To say to be sure to include 0-1 month population segment in the pediatric stud and to suggest May 2014 for final protocol submission.	
June 25, 2008	Phone conversation with James Moore. Comments re pediatric study were sent to Pediatrics Review committee	
June 25, 2008	Meeting: Informal inquiry on status of pending NDA 22,090.	
June 24, 2008	Phone conversation with James Moore. Inquiry re status of NDA 22,090	
June 16, 2008	Phone conversation with James Moore: To communicate an update on review of NDA 22-090 for Eovist	
June 13, 2008	Phone conversation with James Moore: Are there any other issues that need to be addressed from the Bayer side re REMS studies.	
June 12, 2008	Response to FDA information request re labeling for Eovist	eCTD 0040
June 10, 2008	Email to J. Moore-Revised PI, carton and vial labels to FDA, Is June 10, 2008 to provide responses firm date, Request meeting with Dr. Rieves to discuss Administrative items.	
June 9, 2008	Fax to J. Moore-Labeling revisions and specific timelines for Pediatric Study Plan	
June 6, 2008	Phone call from J. Moore-FDA will be sending communication re Draft Labeling and Pediatric Plan	

June 6, 2008	Phone call to J. Moore-Request update on status of NDA 22-090 (Eovist) Review	
June 2, 2008	Quarterly Safety Update on NSF	eCTD 0039
May 29, 2008	Phone call to J. Moore: Request status of NDA review	
May 22, 2008	Phone call to J. Moore to follow-up on Eovist action letter.	
May 19, 2008	Submission of draft labeling for Eovist in response to FDA comments	eCTD 0038
May 16, 2008	Submission of revisions to Eovist draft labeling in eCTD format	
May 16, 2008	Email: Agency has further changes to Eovist Labeling	
May 15, 2008	T-con to discuss Labeling and Post-Marketing Labeling and Pediatric Study Plan with Review Division and Pediatric reviewer(s)	
May 14, 2008	To submit draft labeling to Eovist	eCTD 0037
May 14, 2008	Submission of revised Risk Evaluation and Mitigation Strategy (REMS) and Draft Pediatric Study Plan Outline	eCTD 0036
May 14, 2008	Response to FDA Draft labeling for Eovist	eCTD 0035
May 12, 2008	Follow-up on fax communication re denial of waiver for pediatric studies.	
May 12, 2008	Fax responses on revised Eovist label (2nd draft) and feedback on request for Pediatric studies.	
May 9, 2008	No waiver of pediatric studies for NDA 22-090 per J. Moore of FDA	
May 8, 2008	Response to FDA comments re labeling	
May 7, 2008	Fax from FDA requesting comments on the 6Adverse Reactions of package insert submitted to Agency on May 5, 2008	
May 7, 2008	Provide post approval commitments, specifically outline of post marketing commitments for evaluation of Eovist.	eCTD 0034
May 7, 2008	Follow-up to email sent to James Moore (draft labels for cartons, vials)	eCTD 0033
May 6, 2008	Response to request in re draft carton and vial labels for EOVIST	
May 6, 2008	Request for submission of carton and vial labels for 10 mL presentation today	
May 6, 2008	Follow-up on labeling request received via voice-mail	
May 5, 2008	Proposed modifications to Draft Labeling	
May 2, 2008	To gain concurrence on submission of NDA 22,090 draft labeling.	
April 29, 2008	Discussion of Post Marketing Commitment to evaluate update of Eovist in patients who are taking rifampin.	
April 28, 2008	Phone call to request a t-con to be held on April 29, 2008 re Post Marketing Commitment to evaluate update of Primovist in patients who are taking rifampin.	
April 23, 2008	Phone call to inform J. Moore that responses to statistical inquiry received on April 16, 2008 have been submitted.	
April 23, 2008	Responses to Statistical inquiry received on April 16, 2008	

April 23, 2008	Fax copy of draft labeling was received from FDA	
April 22, 2008	Phone call to inform Mr. Moore of FDA that responses to inquiry from statistical review group will be sent on April 23.	
April 21, 2008	Responses to observations presented on Form 483 at exit meeting on April 2, 2008	
April 18, 2008	Response to CMC inquiry received on April 7, 2008 from CMC review group.	
April 16, 2008	Inquiry regarding location of statistical information in NDA 22-090	
April 11, 2008	Response to CMC inquiry received on April 7, 2008 via email.	
April 11, 2008	To communicate to FDA, Bayer's target date for responses to the 483.	
April 10, 2008	To clarify the impact of the amendment of Module 1.14.1 Draft Labeling section of the NDA 22,090 for 5mL and 7.5mL presentations (in vial and syringe) on review time.	
April 9, 2008	Inquiry from FDA as to status of responses regarding CMC inquiry communicated via e-mail on April 7, 2008.	
April 9, 2008	Response to inquiry received on April 7, 2008 from Statistical review group.	
April 7, 2008	To communicate an inquiry regarding the discrepancy between the labeling section (both PI and container/carton labels) and CMC section of the NDA.	
April 7, 2008	To communicate a statistical inquiry from the Statistical Review group. Appointment of a new Project Manager to NDA 22,090	

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EOVIST/PRIMOVIST SUBMISSIONS LOG

Serial No.	SUBJECT	DATE
40	Information Amendment: Clinical	2/5/04
41	2004 Annual Report	2/6/04
42	2005 Annual Report	2/15/05
43	Type C Meeting Request	10/14/05
44	Submission of Sponsor Package for Type C Meeting	Dec 15, 2005
45	Request for a Type C Meeting	2/8/06
46	2006 Annual Report	2/10/06
47	Type C Meeting Package	3/20/06
48	Letter: erroneous Serial No. assignment	4/25/06
49	Letter: Sponsor's comments on FDA Type C meeting minutes	5/30/06
50	Sponsor's response to clinical comments received on 18 April 2006	6/16/06
51	Pre-NDA meeting request	10/27/06
52	Sponsor's response to Pharm/Tox Comments	11/21/06
53	NSF update	12/1/06
54	Second Pre-NDA meeting request	12/20/06
55	Submission of Sponsor Package for Pre-NDA meeting	12/20/06
56	General Correspondence: Company Name change	11Jan2007
57	2007 Annual Report	2/16/07
58	NSF update	01 March 2007
59	Comments on official preNDA meeting minutes	3/28/07
60	Written response to comments received 13 April 2007	5/01/07
61	Written response to comments received 4 May 2007	5/15/07
62	NSF update	01 Jun2007
63	NSF update	05 Sep 2007
64	NSF update	07 Dec 07
65	200718512GPV, Initial 15-Day IND Safety Report	03 Jan 2008
66	200718512GPV, FU # 1, 15-Day IND Safety Report	14 Jan 2008
67	200811398GPV & 200811248GPV Initial 15-Day IND Safety Report	28 Jan 2008
68	FU #1 200811398GPV & 200811248GPV Initial 15-Day IND	7 Feb 2008

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EOVIST/PRIMOVIST SUBMISSIONS LOG

Serial No.	SUBJECT	DATE
69	Annual report	February 18, 2008
70	Quarterly safety update on NSF	February 29, 2008
71	IND - 20815169GPV 15 day safety report-Initial	March 31, 2008

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 22-090

NDA APPROVAL

Bayer Healthcare Pharmaceuticals
Attention: Ayse U. Baker, Ph.D., MBA
Associate Director
Oncology and Diagnostic Imaging
340 Changebridge Road
Montville, NJ 07045

Dear Dr. Baker:

Please refer to your new drug application (NDA) dated June 29, 2007, received July 2, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Eovist® (Gadoxetate Disodium) Injection.

We acknowledge receipt of your submissions dated July 20, August 10, 17, and 21, September 5 and 27, October 11 and 15, November 1 and 14, December 6, 10, 14, 17, and 18, 2007; January 2, 7, 13, 14, 21, 29, and 30, February 29, March 7 and 27, April 9, 18, and 23, 2008, May 5, 7, 14, 16, 19 and 27, June 12 and 27, 2008.

This new drug application provides for the use of Eovist® Injection for use in magnetic resonance imaging (MRI) of the liver in adult patients to provide contrast in the T1 weighted images to aid in the detection and characterization of focal liver pathologies in pre-surgical evaluation.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

Your application for Eovist® Injection was not referred to an FDA advisory committee because your product is a member of the class of previously approved gadolinium-based contrast agents and the product did not pose unique concerns beyond those applicable to other members of this class.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are deferring pediatric studies for ages 0 to 2 months for this application until additional safety data have been collected. Eovist® is eliminated via the renal and hepatobiliary systems. Hence, impairment or immaturity of these systems, as may importantly occur in patients less than 2 months of age, may increase the risk for serious adverse reactions to Eovist®. Prior to initiation of clinical studies in pediatric patients less than 2 months of age, you must provide nonclinical (animal) data supporting the safety of your product in this patient population. We are deferring studies in pediatric patients > 2 months to 18 years because this product is ready for approval for use in adults and the pediatric studies in this population have not been completed.

Your deferred pediatric study in patients less than 2 months of age is required by section 505B(a) of the FDCA and is a required postmarketing study. However, initiation of this study is contingent upon submission of nonclinical data supporting the safety of the study. These nonclinical data should be obtained from new born animals that model pediatric patients aged less than 2 months. We recommend submission of a protocol for the nonclinical study(ies) prior to the initiation of these studies. In the event your nonclinical data do not support the safety of the pediatric study, we will consider whether a waiver of the pediatric study requirement is appropriate for this population. The status of this postmarketing study in patients less than 2 months of age must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below, as described in your submission of June 27, 2008.

1. Deferred pediatric study under PREA for use in magnetic resonance imaging (MRI) of the liver in pediatric patients ages 0 to 2 months with known or suspected hepatobiliary pathology. This study will obtain evaluable safety and imaging data from at least 10 subjects, however, due to the anticipated rarity of these clinical conditions in this pediatric population, progress towards recruitment will be assessed at one year after study start and the targeted number of patients may require adjustment. Any adjustment in the sample size will be supplied in a protocol amendment that contains supportive information and a request for FDA concurrence. Descriptive statistics will summarize safety and efficacy outcomes. Efficacy determination will be based upon extrapolation from studies in other patient populations.

Protocol Submission:	November, 2011
Study Start:	May, 2012
Final Report Submission:	May, 2014

Your deferred pediatric study in patients ages > 2 months to 18 years is required by section 505B(a) of the FDCA and is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. This required study is listed below, as described in your submission of June 27, 2008:

2. To conduct the study entitled, "An observational study of the administration of Eovist® in pediatric patients who are referred for a routine contrast enhanced liver MRI because of suspected or known focal liver lesions." This study will enroll subjects aged > 2 months to 18 years and obtain evaluable safety and imaging data from at least 50 subjects. Efficacy will be assessed based upon comparison of uncontrasted images to Eovist®-contrasted images. Descriptive statistics will summarize safety and efficacy outcomes.

Protocol Submission:	November, 2008
Study Start:	May, 2009
Final Report Submission:	May, 2013

Submit final study reports to your NDA 22-090. Use the following designator to prominently label all submissions:

Required Pediatric Assessment(s)

POSTMARKETING REQUIREMENTS UNDER 505(o)

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Act of 2007 (FDAAA) amends the FDCA to authorize FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute (section 505 (o)(3)(A), 21 U.S.C. 355(o)(3)(A)). This provision took effect on March 25, 2008.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk, that is, risk for the development of nephrogenic systemic fibrosis (NSF) in patients with renal insufficiency with the class of gadolinium-based contrast agents, of which Eovist® is a member. NSF is a potentially fatal condition. This known risk applies to patients with acute or chronic severe renal insufficiency (glomerular filtration rate, GFR < 30 mL/min/1.73m^2) or patients with acute renal insufficiency of any severity due to the hepato-renal syndrome or in the perioperative liver transplantation period.

Furthermore, the new pharmacogivilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is therefore not sufficient to assess this known serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess this known serious risk and monitor the incidence of NSF among patients with moderate to severe renal insufficiency.

Therefore, based on appropriate scientific data, FDA has determined that you are required, pursuant to section 505(o)(3) of the FDCA, to conduct the following clinical trial:

3. A trial to collect clinical data sufficient to assess the magnitude of risk for the development of NSF with your product among patients with moderate (GFR < 60 mL/min/1.73m^2) to severe renal insufficiency.

The timetable you submitted on June 12, 2008, states that you will conduct this trial according to the following timetable:

Protocol Submission:	October, 2008
Trial Start Date:	December, 2008
Final Report Submission:	December, 2013

Submit the protocol to your IND 54,875 with a cross-reference letter to this NDA 22-090. Submit all final report(s) to your NDA 22-090. Use the following designators to prominently label all submissions, including supplements, relating to this postmarketing clinical trial as appropriate:

Required Postmarketing Protocol under 505(o)
Required Postmarketing Final Report under 505(o)
Required Postmarketing Correspondence under 505(o)

You are required to report periodically to FDA on the status of this clinical trial pursuant to sections 505(o)(3)(E)(ii) and 506B of the FDCA, as well as 21 CFR 314.81. Under section 505(o)(3)(E)(ii), you are also required to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue associated with your product.

POSTMARKETING COMMITMENT

We remind you of the following postmarketing clinical trial commitment agreed upon in your submission dated June 12, 2008:

4. To conduct a single center crossover study to evaluate the possible influence of Erythromycin as an example of an inhibitor of the organic anion transporting peptide on the hepatocyte uptake of Eovist® in liver MR imaging in healthy subjects.

Protocol Submission:	December, 2008
Trial Start Date:	May, 2009
Final Report Submission:	May, 2010

Submit clinical protocols to your IND 54, 875. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA 22-090. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical trials, number of patients entered into each trial. All submissions, including supplements, relating to these postmarketing commitments should be

prominently labeled **"Postmarketing Commitment Protocol", "Postmarketing Commitment Final Report", or "Postmarketing Commitment Correspondence."**

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the agreed upon labeling. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for approved NDA 22-090."

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the agreed upon text for the carton and immediate container labels as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (October 2005).* Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission **"Final Printed Carton and Container Labels for approved NDA 22-090."** Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see www.fda.gov/cder/ddmac.

Please submit one market package of the drug product when it is available.

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
Suite 12B05
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at www.fda.gov/medwatch/report/mmp.htm.

If you have any questions, call James Moore, Regulatory Project Manager, at (301) 796-2050.

Sincerely,

{See appended electronic signature page}

Karen Weiss, M.D.
Deputy Director
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure